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BLAIR-BELL MEMORIAL LECTURE *

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Hydatidiform Mole and Chorion-epithelioma

BY

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MR. PRESIDENT, members of the Council, ladies and gentlemen.

I am deeply conscious of the honour and distinction that the College has conferred on me by electing me a Blair-Bell Memorial Lecturer. By his forethought and generosity in endowing these lectureships the late Professor William Blair-Bell has assured the continuation in some part of that assistance and encouragement to his junior colleagues that he gave so liberally during his lifetime.

Mr. Jeffcoate,[1] happily chosen from Blair-Bell's own school to deliver the inaugural lecture, enhanced its success by a personal memoir of our first President. I am unable to employ a similar preface to the second lecture, as I had only a very limited personal acquaintance with Blair-Bell, but I should like to express my indebtedness to his extensive original publications. Some of them contribute to our knowledge of hydatidiform mole and chorion-epithelioma, and to these I will refer later.

It is well known to most of you that Blair-Bell's researches were continually directed towards the elucidation of two great problems, namely, the hormonic control of the organs of sex, and the

* Delivered at the Royal College of Obstetricians and Gynaecologists.

aetiology and treatment of cancer, and it is apposite that my subject this evening requires a consideration of both and might well have received his approval.

As hydatidiform mole and chorion-epithelioma are diseases but rarely encountered in clinical practice, a comprehensive knowledge of their various clinical, pathological and biological manifestations can rarely be acquired from individual experience.

According to leading authorities on veterinary obstetrics hydatidiform mole occasionally occurs in domestic animals, especially in the cow, but it would seem to be even rarer than in the human. They do not record the occurrence of chorion-epithelioma.

Colonel Hamerton, of the Pathological Department of the London Zoological Gardens, has kindly obtained for me the information that there is no recorded instance of either condition having occurred in a pregnancy of a wild animal in captivity in these gardens during the last 20 years.

My lecture this evening is based on my limited personal experience of these conditions, supplemented by *data* derived from an extensive review of the world literature, and from an analysis of case records from the London Hospital, comprising 100 consecutive cases of hydatidiform mole treated during a period of 33 years, 1905 to 1937; and 26 consecutive cases of chorion-epithelioma treated during a period of 53 years, 1885 to 1937. Thus the incidence in this large teaching hospital is on an average 3 cases of hydatidiform mole a year, and 1 case of chorion-epithelioma in 2 years.

Hydatidiform mole is a disease of ancient recognition. I have tabulated in chronological order a few dates of interest in its history.

TABLE I.

HYDATIDIFORM MOLE—HISTORICAL.

	B.C.	
4th to 5th century	?	Hippocrates.
	A.D.	
6th century	?	Aetius of Amida.
13th century	1276	Story of the Countess Henneberg.
18th century	1752	William Smellie (and M. Lamotte).
19th century	1827	Velpeau and Madame Boivin
	1853	Virchow.
	1895	Marchand.
20th century	1929	Rössler, and Zondek.

In his treatise on "Air, Water and Places"[2] Hippocrates attributes dropsy of the uterus to the drinking of unhealthy water.

Writing "De Uteri Hydropii"[3] in his sixteenth book, Aetius of Amida makes an unmistakable reference to the condition, for he says, "when the menses have been suppressed for some time and the patient has not become pregnant, the uterus becomes filled with humour, and small bladder-like objects are developed in the fluid".

The sometimes misquoted story of the Countess Henneberg[4] is derived from an inscription on a marble tablet which still is, or at least was, in the church of Lonsdunen, near Leyden. The preface may be translated from the original Latin :—

> Lo! I shall reveal to you an occurrence exceedingly extraordinary and worthy to be remembered, the like of which has not been vouchsafed since the beginning of the world.

Below it is then related that Margaret, wife of Hennan, earl of Henneberg, being about 40 years old, on Easter Day, 1276, was brought to bed of 365 children, who were baptised in two brazen basins by Guido, suffragan of Utrecht. The males, how so many there were of them, were christened John, all the daughters Elizabeth, who all, together with their mother, died on the same day, and with their mother lie buried in this church of Lonsdunen.

This supernatural infliction is accounted for on the principle of retributive justice, for we are informed that the Countess, being solicited for alms by a poor woman who was carrying twins, shook her off with contempt, declaring that she could not have them by one father. Whereupon the poor woman prayed to God to send her as many children as there were days in the whole year, which came to pass as is briefly recorded in this tablet for perpetual recollection. It seems probable that the noble lady sank from flooding after a spontaneous abortion of a hydatidiform mole.

William Smellie,[5] under the title of "Hydatids of the uterus", has given us two most realistic descriptions of the spontaneous abortions of hydatidiform moles. In addition he quotes from the obstetric writings of a contemporary colleague, Monsieur Lamotte, who, in his sixteenth observation, gives an account of a woman who, imagining herself gone with a child about 5 months, was delivered of a mole or something of that nature, as big as two fists, composed of an infinite number of membranes, which held together like a swarm of frogs. This is the earliest reference I have been able to find of the association of the two terms, hydatid and mole.

The first recognition of the hydatids being cystic dilatations of the chorionic villi is attributed to Velpeau and Madame Boivin[6] in 1827.

Throughout all but the last few years of the nineteenth century the name hydatidiform mole continued to truthfully express the prevalent conception of the condition, mole inferring a degenerate, dead or blighted ovum, and the qualifying adjective hydatidiform indicating a distinction from other hydatids which it resembled, now known to be parasitic in origin.

In 1853 Virchow[7] still considered the essential lesion was a degeneration, mxyomatous in character, affecting the stroma of the villi.

The modern conception of excessive proliferation of syncytial and Langhan's cells as the primary morbid change originated with a monograph published by Marchand in 1895. The name hydatidiform mole is, therefore, no longer as truly descriptive as formerly, for the foetal ectoderm is proliferating rather than degenerating, and on occasion the foetus may survive even to term with the birth of a living healthy child.[8, 9]

In 1929 Fels,[10] Ehrhart,[11] Roessler[12] and Zondek[13] were the first to demonstrate marked excess of gonadotropic hormone in the urine of patients suffering from this condition compared with the amount usually excreted in normal pregnancy. This discovery quickly resulted in the use of quantitative assays in diagnosis and in the after care of these patients.

I have included in my series only cases of hydatidiform mole, or vesicular degeneration of the chorion, that were diagnosed macroscopically. Minor degrees of vesiculation of chorionic villi have been recognized sporadically by histologists for many years, but Meyer,[14] investigating a large number of spontaneous abortions with the aid of the dissecting microscope, demonstrated similar changes in some or all of the chorionic villi in nearly one-third of the specimens examined. I have omitted all such cases from my series.

In 97 cases no uterine content other than molar tissue was recognized. In 2 cases there was a twin pregnancy, a normal foetus and placenta co-existing with a hydatidiform mole, and in 1 case there were multiple focal areas of vesicular degeneration in a placenta with a well-formed foetus attached. The development of the foetus in each case was about 14 weeks.

Aetiology.

The view that the condition is a primary disease of the ovum

is the one most consistent with the evidence at present available. The most recent estimation of its frequency is that of Das[15] of Calcutta, who calculates its average incidence in seven obstetric hospitals in Great Britain as 1 in 835 of their admissions. Such hospitals, however, have rarely sufficient accommodation to admit cases of abortion, even those occurring in their booked cases, and it is probable that this figure is an underestimate of the actual incidence in all pregnancies. More cases are encountered in gynaecological than in obstetric clinics.

In my series the age incidence is wide, but confined to the fertile period. Three patients were under 20, but one-third of the patients were 40 or more. In 26 per cent the molar pregnancy was a first pregnancy, but the average fertility was 4 pregnancies and 0.6 miscarriages. Only one patient had had a previous molar pregnancy, and a follow-up of more than half of these patients has not revealed any subsequent molar pregnancies.

Essen-Moller[16] has published a collection of 18 cases of repeated molar pregnancy, but the possibility may be safely minimized in discussing future pregnancies.

Clinical history of Hydatidiform Mole.

In nearly 75 per cent of my cases the presenting symptom was abnormal uterine haemorrhage following a period of amenorrhoea up to 12 weeks in duration. In 8 patients there was not any period of amenorrhoea, and in 20 patients the amenorrhoea was prolonged, lasting in 2 cases as long as 40 weeks.

In 1924 Blair-Bell[17] published a description of a hydatidiform mole associated with 10 months of amenorrhoea, which was removed by abdominal hysterotomy. It enlarged the uterus only to the size of a 12 weeks' pregnancy. It exhibited many of the features usually ascribed to a carneous mole in addition to hydatidiform vesiculation. The term hydatidiform mole is truly descriptive of this definite though relatively infrequent type,[18] which has atypical clinical, pathological and biological features. It can only be diagnosed by biopsy.

Clinical examination of Hydatidiform Mole.

The uterus is typically larger than it should be in relation to the calculated duration of pregnancy. Information relevant to this physical sign was available in 57 cases in my series in which an escape of molar tissue from the uterus had not occurred. In 72 per cent it was bigger than it should have been; in 12 per cent it was the correct size; and in 16 per cent it was abnormally small. The excessive enlargement in most cases is attributable to the

excessive volume of the cystic chorion rather than to concealed haemorrhage. Partial or complete necrosis of the mole with its continued retention *in utero* accounts for the absence of this physical sign in about 1 case in 4 in my series, and for the publication of small collections of cases, such as that of Briggs,[19] in which the presence of an abnormally small uterus is predominant.

The presence of signs of pregnancy toxaemia at an unusually early period of gestation may be of significance. In 56 of my cases the urine was examined, and in 21 patients, that is in 37 per cent, albumin was present. In 8, that is 14 per cent, it was present in large amounts. I have omitted all cases in which blood was also present, as it indicates contamination from the genital tract. In many the specimen examined was obtained by catheter. I cannot associate albuminuria with any exceptional malignant features in the moles occasioning it. In a few patients the presence of oedema and hyperpiesis was also recorded.

Marchand and his contemporaries recognized a frequent association of cystic enlargement of the ovary with hydatidiform mole. Much speculation on the significance of the association pervades the literature since that time, and it is only during the last 10 years that increasing knowledge of the sex hormones has provided a satisfactory explanation.

It is more in harmony with our present knowledge to consider not only the association between hydatidiform mole and ovarian cystomata, but also the association between hydatidiform mole and excessive luteinization of the ovaries. In Table II I have classified all the relevant information I can collect from my series.

TABLE II.

1. *Association of hydatidiform mole with ovarian cystomata.*		
A. Palpated clinically in 8 out of 100 patients		8 per cent
B. Visible at laparotomy (mole still *in utero*) in 8 out of 10 patients		80 per cent
2. *Association of hydatidiform mole with excessive ovarian luteinization demonstrable at biopsy.*		
14 ovaries removed from 8 patients (mole still *in utero*).		
Large bilateral multilocular lutein cystomata	2 patients	100 per cent
Small bilateral multilocular lutein cystomata	3 patients	
Small unilateral multiocular lutein cystomata	3 patients	
In case 89 (aged 45) 1 ovary did not show any lutein tissue.		
Ovaries clinically enlarged, 5 from 3 cases.		
Ovaries not clinically enlarged, 9 from 5 patients..		

In group 1 (A) there were three patients with large bilateral multilocular luteal cystomata. The largest is of one ovary from case 48. It measured 23 × 13 × 7 cms. and it was composed of luteal cysts up to 6 cms. in diameter, with a few intervening solid luteal bodies up to 1.2 cms. in diameter. The luteal cells are all apparently derived from the cells of theca interna. In the other 5 cases small unilateral cysts up to the size of a tennis ball were palpated on bimanual examination.

The occurrence of excessive lutein formation in ovaries which are not enlarged I would emphasize by a more detailed reference to case 64.

Twelve weeks' amenorrhoea was associated with uterine enlargement to the size of a 28 weeks' pregnancy. Death from haemorrhage occurred prior to the abortion of the mole, and at the post-mortem examination the ovaries were of average normal size, (right 2.1 × 1.8 cms; left 2.3 × 1.4 cms). On section, however, both contained several corpora lutea showing slight central cystic changes. It is apparent from these findings that luteinization of the ovaries in excess of that associated with normal pregnancy occurs in one or both ovaries, with or without their cystic enlargement, in association with the vast majority of molar pregnancies. It represents an atypical pregnancy reaction in the human ovary. This pregnancy reaction is produced in a similar manner to those in the ovaries of mice and rabbits in positive Aschheim-Zondek and Friedman reactions. The stimulus in each case is chorionic gonadotropic hormone, but in hydatidiform mole this often is applied in high concentration for a period of many weeks. The type of ovarian response, excessive luteinization without enlargement, small cystic enlargement, or gross cystic enlargement, will depend on the duration of the existence of the mole, its physiological activity in hormone production and on the susceptibility of the patient's ovaries to the gonadotropic hormone stimulation.

In my series the type of response appears to be related to the age of the patient. The three examples of large bilateral multilocular luteal cystomata occurred in patients aged 20, 22 and 24 respectively.

Only one of the five patients with a cystic ovary discovered clinically was over 30 years of age. She subsequently developed secondary chorion-epithelioma.

The one ovary of the 14 removed and examined histologically that did not contain any luteal tissue was from a patient aged 45 years.

Hydatidiform Mole. Biopsy of material escaping from the uterus.
Typical hydatidiform vesicles had either escaped externally or were found in the lower genital tract in 20 patients at the time of admission, and thereby a certain diagnosis was made possible.

Hydatidiform Mole. Radiological Examination.
Radiography of the uterus was employed in 5 of the more recent cases in my series. In each the report was "no foetal parts seen." Case 94 deserves special mention. A history of 16 weeks' amenorrhoea was associated with the presence of a uterus the size of a 22 weeks' pregnancy. The radiological report, "no foetal parts seen," in conjunction with other findings, led to abdominal hysterotomy as the method of treatment. Incision of the uterus revealed a mass of hydatidiform mole and a normal pregnancy of about 14 weeks' development. Had the excessive uterine enlargement been due to the existence of a normal twin pregnancy of similar development, with two foetûs not yet demonstrable radiologically, a serious error would have been committed. The difficulty of distinguishing between a normal twin pregnancy and hydatidiform mole is increased by the exceptionally high gonadotropic hormone excretion often associated with it. I have had experience of an Aschheim-Zondek positive test in a dilution of 1/200 in such a case.

Hydatidiform Mole. Gonadotropic Hormone Assays.
Assays using the Aschheim-Zondek technique with varying dilutions of urine have been employed as an adjunct to diagnosis in 6 of the last 11 cases in my series, in which no part of the mole had escaped from the uterus.

In 5 a positive reaction was obtained in a dilution of 1/200, in one case in a dilution up to 1/800. In the remaining case a negative reaction was obtained in undiluted urine. The positive reactions in a dilution of 1/200 resulted from the injection of total amounts of diluted urine varying from 2.4ccs. to 3ccs. They, therefore, represent a urinary output varying between 66,000 and 83,000 mouse units per litre of urine.

In 1937 Zondek[20] once again raised the level of gonadotropic hormone production which he considered must be demonstrated in order to justify a diagnosis of hydatidiform mole on assay alone. If 200,000 mouse units per litre of urine can be demonstrated repeatedly in the urine and a positive reaction can be demonstrated in the cerebrospinal fluid, preferably in dilution, then an unqualified diagnosis of hydatidiform mole or chorion-epithelioma can be made.

The inferences which can be safely made from high gonadotropic hormone assays have been limited by repeated demonstrations of the existence of a period of high production in association with normal pregnancies. This period is usually of about 3 weeks' duration, with a maximal level or peak of production about the sixtieth day of gestation. Levels of urinary hormone excretion such as are represented by my positive tests of 1/200, may occur. Such levels are even more frequent in multiple pregnancy.

Dr. Boycott,[21] working in conjunction with Professor Browne at University College Hospital, has given me permission to show some of her results with quantitative Friedman tests in cases of normal pregnancy at about this peak period.

TABLE III.

*Quantitative Friedman assays of urinary excretion of gonadotropic hormone early in normal pregnancies.**

No. of cases	Duration of pregnancy in weeks	Friedman reactions in dilution	
		Positive	Negative
1	6		1/50
2	10 to 12	1/150	1/200
		1/100	1/200
2	12 to 14	1/50	1/100
		1/100	1/150
1	14		1/50

* By permission of Dr. Boycott, Research Biologist, Obstetric Unit, University College Hospital.

It is apparent that as a method of absolute diagnosis of the presence of morbidly active chorion-epithelioma quantitative hormone assays have failed to realize initial expectations, but assays far below Zondek's present standard of absolute diagnosis remain of great value, and constitute one of the six sources of information on which a diagnosis may be made.

In 2 further cases in my series hormone assays were made on catheter specimens of urine obtained during the abortion of moles. A positive reaction in undiluted urine was obtained in both cases, but reactions in dilutions of 1/25 and 1/100 respectively were negative. These findings are at variance with those also communicated to me by Dr. Boycott on urine obtained from a patient of Professor Young during abortion, which was found

to have a positive Friedman's reaction in dilution of 1/600 and negative 1/700.

The literature contains a number of recorded cases of abnormally low or negative hormone assays in association with hydatidiform mole. They probably represent examples of delayed or missed abortion of separated moles similar in type to that previously described, published by Blair-Bell in 1924. My own case of a negative Aschheim-Zondek reaction in undiluted urine associated with a hydatidiform mole was one in which a history of 22 weeks' amenorrhoea was associated with the presence of a carneous mole with hydatidiform vesicles scattered through it in the uterus, the total size was about that of a large walnut.

Hydatidiform Mole. Exploration of the uterus.

This was the confirmatory method of diagnosis in all cases in which there had not been any escape of vesicles from the uterus, before admission or during in-patient observation and investigation.

Hydatidiform Mole. Differential Diagnosis.

The commonest error in diagnosis was that of regarding the abdominal swelling as an ovarian or uterine neoplasm. There were ten such errors in this series, most of them being made in patients over 40 years of age, in whom short periods of amenorrhoea and irregular uterine hæmorrhage were not regarded as due to pregnancy. In two other cases the diagnosis of ovarian cyst and normal pregnancy was correct in so far as there were bilateral ovarian cysts. The associated pregnancy, however, was abnormal.

In 13 cases the uterus was explored, the correct diagnosis having been previously arrived at prior to any escape of the uterine contents. The relative frequency of such correct diagnosis has undoubtedly increased in recent years since radiography and hormone assays have been employed.

Treatment of Hydatidiform Mole

The various forms of treatment adopted for the patients in this series have been analysed in Table IV.

Blood transfusion was not given in any case. In 4 patients an intravenous saline infusion was carried out.

This analysis very clearly demonstrates the conservative character of the treatment employed; only 7 per cent of the

patients have been treated by the radical method of removal of the uterus.

The real merit of a form of treatment must ultimately be judged by the mortality associated with it, and by the frequency and severity of complications following it, when compared with other available methods.

TABLE IV.

HYDATIDIFORM MOLE—TREATMENT.

Medical treatment.		
Supervision of spontaneous complete abortion of the mole when medical was the only form of assistance being employed		12 cases
Surgical treatment by vaginal operation.		
(*a*) Induction of abortion completed spontaneously	7	
Completed by digital evacuation of uterus	6	13 cases
(*b*) Exploration of uterus followed by immediate digital evacuation of the mole		24 cases
(*c*) Digital evacuation of retained mole in case of incomplete abortion, 30 spontaneous, 1 after induction		31 cases
(*d*) Diagnostic exploration of uterus following recent abortion, spontaneous or therapeutic, prior to admission ...		10 cases
(*e*) Vaginal hysterotomy		1 case
By abdominal operation.		
(*a*) Hysterotomy		1 case
(*b*) Subtotal hysterectomy		3 cases
(*c*) Total hysterectomy		4 cases
Admitted moribund, died, mole still *in utero*		1 case

In this series of 100 cases there has been only 1 death (case 64). The patient's last menstrual period was 3 months before admission. There was a history of slight vaginal bleeding for 8 weeks, and of severe hæmorrhage for 24 hours, blood having soaked through two mattresses. She was admitted moribund from anaemia. Saline was infused intravenously, but she died before a blood transfusion could be given. At the post-mortem examination the uterus, which reached 2 inches above the umbilicus, contained a large partly-separated hydatidiform mole and the cause of death, acute anaemia from haemorrhage, was confirmed.

Hydatidiform Mole. Mortality.

This primary mortality of 1 per cent is the lowest yet recorded

in any considerable series. It may well be fortuitous in a series of only 100 cases, but it compares favourably with a mortality of 1.4 per cent just published by Albert Mathieu[22] for a collection of 576 hydatidiform moles amassed from 179 articles published in the literature during the 3 years, 1935, 1936 and 1937. Sherman's[23] consecutive series of 78 cases from the Lying-In Hospital, New York, with a mortality of 2.5 per cent, is more directly comparable with my own.

Mathieu contrasts the recent low mortality with a mortality of approximately 12 per cent in cases amassed from the literature prior to 1930. He attributes the marked improvement to earlier diagnosis and better treatment. Personally, I do not think the published material prior to and since 1930 is entirely comparable. Before that time cases of hydatidiform mole were published when the patients exhibited unusual clinical features or interesting complications, straightforward orthodox cases remaining in obscurity. Since 1930 cases of hydatidiform mole of no outstanding clinical interest have merited publication because of the hormonal investigations made upon the patients.

I can refer only to a few of the most important complications following hydatidiform mole.

1. *Puerperal Pyrexia.*

The 86 temperature charts of the convalescent period which are available I have divided into groups in Table V.

Torsion is a well-recognized complication of large luteal cystomata, and may necessitate surgical treatment. Suppuration, as in case 1 in my series, is much less common.

TABLE V.

HYDATIDIFORM MOLE—PUERPERAL PYREXIA.

		Number	per cent
Convalescence non-febrile		38	44.0
Moderate pyrexia not exceeding 14 days' duration		39	45.3
Severe pyrexia:			
Parametritis	1		
Pyaemia	2		
Septicaemia	5		
Bilateral suppurating luteal cysts ...	1	9	10.5
		86	

2. *Secondary Haemorrhage following the Evacuation of Hydatidiform Mole.*

Seven patients were primarily treated by hysterectomy. None of these developed post-operative haemorrhage as a complication. One patient died before the mole was expelled.

Out of the remaining 92 patients 17 developed secondary uterine haemorrhage within a few weeks of the expulsion of the mole, i.e. 18.4 per cent. In each of these 17 patients the uterus was explored or re-explored and fragments of tissue were sent for microscopic biopsy. The histological reports have been grouped in Table VI.

TABLE VI.

HYDATIDIFORM MOLE—SECONDARY HAEMORRHAGE.
Biopsy after diagnostic curettage.

Report	Number of patients
Chorion-epithelioma	7 (in 5 C.E. confirmed)
Hydatidiform mole, probably malignant	3
Hydatidiform mole, benign	3
Multinucleate giant cells, such as are seen in normal pregnancy	1
No chorionic elements	3
	17

In all the cases reported as chorion-epithelioma panhysterectomy was performed. In 5 cases its presence was confirmed. In the uterus after removal in the other 2 cases a growth was not found. In 2 patients reported as having hydatidiform mole, probably malignant, panhysterectomy was performed; a growth was not found in either uterus. In the other patient a subsequent curettage was negative and hysterectomy was not performed. Further treatment was not carried out in any of the other cases, and none of the patients subsequently developed chorion-epithelioma. In short, the biopsy of 10 out of 17 cases of secondary haemorrhage, i.e., 58.8 per cent, suggested malignancy, and half of these, 29.4 per cent were subsequently proved to have chorion-epithelioma developing in the uterus.

The last complication of hydatidiform mole which I will mention is chorion-epithelioma. It most commonly develops within 6 months of the abortion of the mole, but it is also

recognized as occurring prior to its abortion and after a latent interval of 2 or more years.

It is extremely difficult to assess the frequency of this complication. Blair Bell frequently referred to healthy chorionic epithelium as a normally malignant tissue.

Dr. Lumsden,[24] Professor of Cancer Research at the London Hospital, has defined malignant cells as body cells which (a) have more or less lost their differentiation; (b) have the power of invading other tissues; and (c) are able to multiply indefinitely. Various normal cells have one or possibly two of these characteristics, but any cell which has all three is a malignant cell. Normal chorionic epithelium has never developed differentiation, and it certainly has the power of invading other tissues. Two features of this normal invasive power I would emphasize: (i) its inherent disposition to penetrate maternal blood-vessels with spontaneous separation of masses of epithelium or even whole villi as vascular emboli; and (ii) the infiltration of the myometrium subjacent to the implantation site by trophoblastic elements resembling mono-or multinucleated masses of syncytium. These cells, however, do not multiply indefinitely, and it is evident that after the termination of a pregnancy that a physiological destruction of its deeply penetrating and embolic remnants must occur.

The presence of malignant changes in this unique tissue can only be assumed if the degree of epithelial proliferation, infiltration, permeation and embolic dissemination is in excess of the normal. The very varying pictures presented by hydatidiform mole and chorion-epithelioma are satisfactorily explained if we also recognize degrees of neoplastic metaplasia: (i) adenomatous hyperplasia; (ii) pre-carcinomatous hyperplasia; (iii) true chorion-epithelioma. These degrees may be recognized in the histological examination of a molar abortion, in the fragments of tissue from a diagnostic curettage, in the proliferation, infiltration and permeation of chorionic epithelium in the uterine wall, and in emboli lodged in other tissues and organs.

Atypical invasiveness is demonstrable (a) when excessive extravasation of blood occurs at the site of penetration of blood-vessels; (b) when abnormal permeation of vessels is visible. It is evident that such permeation may be by villi showing adenomatous or carcinomatous hyperplasia of their epithelium, or by epithelial masses unassociated with this formation; (c) by excessive necrosis of adjacent tissues and by their infiltration by chorionic elements other than those previously mentioned, or by these in excessive degree. Some so-called penetrating, infiltrating

and perforating moles should, I think, be included as examples of true chorion-epithelioma.

Only 9 cases of spontaneous perforation of the uterus by a hydatidiform mole have been recorded in the literature, one of them being case 70 in this series. Of these, 3 patients died, and in one at least multiple pulmonary metastases were present at post-mortem. This perforating mole and one penetrating mole, the mole invading the entire myometrium as far as the peritoneum, I include as having developed the complication of chorion-epithelioma. Both show permeation by villi with carcinomatous hyperplasia, and in addition, infiltration of syncytial and Langhan's cells between muscle bundles and associated excessive extravasation of blood and tissue necrosis.

Embolic dissemination of normal chorionic epithelium is an accepted occurrence. It follows that embolus of epithelium or villi from benign or malignant moles may also occur, in addition to emboli from malignant chorionic epithelium without villous formation. Thus a metastasis may be benign, somewhat malignant, or extremely malignant. In one fatal case of secondary carcinoma (case 23) multiple metastases were present at post-mortem. In one other case spontaneous resolution of a vaginal metastasis occurred after hysterectomy for secondary chorion-epithelioma. In no other case is there proof of the existence of metastases, but in case 91 slight recurrent haemoptysis preceded the abortion of an apparently benign mole. Radiography of the chest was negative, but a positive pregnancy test persisted for $4\frac{1}{2}$ months and then became negative, and the patient remains well 4 years later.

The next table, Table VII, summarizes the incidence of secondary malignant metaplasia in the hydatidiform moles constituting this series.

A secondary curettage was carried out in 47 cases. In 17 the indication was secondary haemorrhage (Table VI). In the remaining 30 it was carried out as a diagnostic measure to confirm or exclude early chorion-epithelioma, and was most commonly performed about 6 weeks after the mole had been evacuated. In none of these 30 patients was chorion-epithelioma demonstrated, but one died about 6 months later from disseminated chorion-epithelioma, (case 23).

The incidence is 8 per cent in the series as a whole, but if one excludes the 7 cases in which primary hysterectomy was performed, and the one patient who died with the mole still *in utero*, the incidence is 8 cases out of 92 in which secondary chorion-

epithelioma of the uterus could have developed, that is, 8.6 per cent.

TABLE VII.

HYDATIDIFORM MOLE—SECONDARY MALIGNANT METAPLASIA.

Examination of primary products of abortion.

No. of cases	Histological report	Subsequently developed chorion-epithelioma	
		No.	Per cent
51	Hydatidiform mole, benign	3	6
15	Hydatidiform mole, probably malignant	3	20
2	Hydatidiform mole, malignant, infiltrating myometrium	1	50
1	Perforating hydatidiform mole, report on uterus after removal	1	
		8	

Control of after care with hormone assays: in 10 out of the last 11 cases in my series hormone assays have been employed.

In 5 cases the assay was negative in undiluted urine on the first occasion it was made, 14 days, 24 days, 4 weeks and 7 weeks after abortion of the mole, and 8 days after a panhysterectomy respectively. In 4 cases the first test was positive in undiluted urine only, 3 days, 8 days, 7 weeks and 5 months after abortion respectively. In one case (case 96) twin pregnancy, hydatidiform mole and normal gestation, very completely removed by abdominal hysterotomy, the positive reaction in dilution of 1/25 was obtained 6 weeks after abortion; a positive reaction in undiluted urine 10 weeks after abortion and a negative reaction in undiluted urine 16 weeks after abortion. In 6 patients there were bilateral moderate cystic enlargement of the ovaries.

CHORION-EPITHELIOMA

This disease, unlike hydatidiform mole, has only been recognized in recent years. In the ensuing tables I will demonstrate a few points of clinical interest which have emerged from a study of my series of 26 consecutive cases.

The condition of chorion-epithelioma originating in a teratoma of the testis was first described by Schlagenhauffer [25] in 1902. The histological picture presented is very similar to that found in chorionepithelioma originating from a pregnancy in the female. It seems to have a greater tendency to lymphatic metastases.

CHORION-EPITHELIOMA, 26 CASES.
London Hospital, 1885 to 1937.

Aetiology	Number of cases
Recent hydatidiform pregnancy	8
Recent miscarriage	7
Nature of recent pregnancy unrecorded	5
Recent full-time labour	4
Recent teratoma of testis	2
	26

CHORION-EPITHELIOMA, 24 CASES (FEMALE).
London Hospital, 1885 to 1937.

Site of primary growth	Number of cases
Body of uterus	17
Body of uterus and cervix	1
Cervix	1
Fallopian tube	1
No primary growth in genital tract ...	4
	24

Cases without a primary focus in the genital tract probably resulted from spontaneous resolution of the primary focus followed by failure to completely resolve a metastasis, the residue subsequently overcomes the factors inhibiting its development and becomes a focus of a generalized dissemination.

CHORION-EPITHELIOMA, 24 CASES (FEMALE).
London Hospital, 1885 to 1937.

Prognosis	Number of cases	Per cent
Known to have survived for not less than 5 years	8	33⅓
Untraced, probably survived	2	
Known to have died	14	
	24	

Six of the eight patients developing chorion-epithelioma after hydatidiform mole are known to have survived in good health for more than three years. All 4 cases following labour proved fatal.

CHORION-EPITHELIOMA, 24 CASES (FEMALE).
London Hospital, 1885 to 1937.

Age incidence	Number of cases
Under 20 years	1
20 to 29 years	6
30 to 39 years	9
40 to 49 years	6
50 years and over	2
	24

Four were primigravidae, 18 multiparae, 2 unrecorded

CHORION-EPITHELIOMA, 24 CASES (FEMALE).
London Hospital, 1885 to 1937.

Immediate cause of death in 14 cases known to have ended fatally	Number of cases
Cerebral metastases	5
Septicaemia	4
Post-operative haemoperitoneum ...	4
Dyspnoea, massive pulmonary metastases	1
	14

In the 2 male cases cachexia was the presenting feature.

CHORION-EPITHELIOMA, 24 CASES (FEMALE).
London Hospital, 1885 to 1937.

Duration of illness.

In the 10 probably surviving patients the duration of symptoms attributable to chorion-epithelioma averaged 8 weeks prior to the date of admission.

In the 14 patients who died the average duration of the symptoms was 13 weeks prior to the date of admission.

An operation was not considered possible in 7 cases (1 patient had had sub-total hysterectomy prior to admission). Abdominal panhysterectomy was possible in 2 cases, 1 patient died a month later of pyaemia, and had secondary metastases in the lungs, femur

and in blood-clot in the heart. (C.E. case 4.) The other died on the post-operative 19th day from a cerebral metastasis known to have been present before operation. Laparotomy resulted in fatal haemoperitoneum in 4 cases, the haemorrhage resulting from trauma inflicted by gentle manipulation exceedingly vascular friable growth in the pelvis in 3 cases, in the liver in 1 case. The remaining patient had a vaginal hysterectomy. The operation could have been performed 3 months earlier, but a vaginal metastasis was reported as squamous carcinoma of the vagina. Re-examined later the diagnosis was corrected to that of chorion-epithelioma.

A post-mortem examination, not always complete, was obtained in all 14 cases. Pulmonary metastases were present in 9, that is 64.3 per cent. Vaginal metastases were present in 7 (plus 1 surviving), 50 per cent. Cerebral metastases were present in 4, 28.6 per cent. Hepatic, intestinal, renal, suprarenal, cardiac, splenic, ovarian, and osseous metastases were each present in 3 cases, 21.4 per cent.

Isolated cases of spontaneous resolution of malignant neoplasms are from time to time recorded in the literature. Such cases have been recorded more frequently in cases of chorion-epithelioma than in any other type of neoplasm. Spontaneous resolution of the primary growth may, however, be followed after an interval by development of secondary metastases.

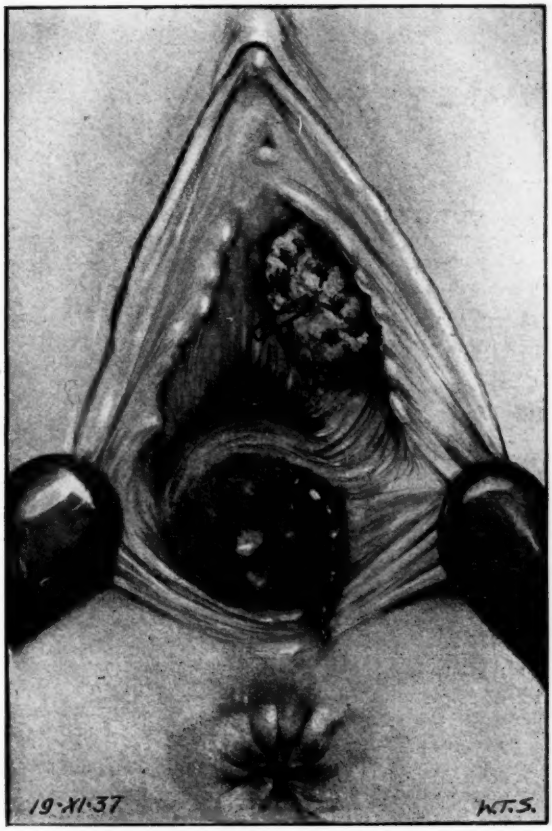
I have been fortunate in having a patient under my care rather more than a year ago, in the Soho Hospital for Women, in whom I was able to observe a spontaneous resolution of a secondary vaginal metastasis of chorion-epithelioma which developed soon after a normal labour at term. I have observed this patient clinically and by means of hormone assays up to the present time, and an abstract of her case-record should establish greater credence for previously published cases of spontaneous resolution in which it was impossible to obtain as complete macroscopic and microscopic confirmation of the diagnosis.

The patient, aged 30 years, had had 5 normal labours, the last 38 days before admission to hospital. This fifth confinement was conducted by a midwife, who stated that the third stage of labour was quite normal and the placenta and membranes complete on examination after expulsion. On the twelfth day of the puerperium a moderate secondary post-partum haemorrhage occurred, and was followed by further intermittent losses. On the twenty-fourth day of the puerperium a small purple, grape-like mass was first noticed at the vaginal orifice.

On the forty-first day of the puerperium examination under anaesthesia in the lithotomy position revealed two lower vaginal metastases of chorion-epithelioma. The anterior metastasis measured 3 cms. anteroposteriorly and 2 cms. from side to side, and projected about 1.25 cms. above the surrounding mucous membrane. It was situated partly behind the left half of the urethra, and partly to its left side. The cervix was ulcerated, granular and greenish-yellow in colour. The posterior metastasis was somewhat dome-shaped, 3.5 cms. in diameter, of a purplish cyanotic colour, and only slightly ulcerated on its left border, which bled immediately on gentle palpation. There was no palpable enlargement of the inguinal lymphatic glands. Some blood-clot projected from the cervix, the canal of which was sufficiently patent to admit the index finger. The lower pole of a small polypoid mass attached to the fundus could be felt. The uterus was slightly retroverted and a sound passed $3\frac{3}{4}$ inches. The ovaries were not palpably enlarged. Fragments were gently removed from the lower pole of the uterine polyp for histological examination. The liver and spleen were not palpable. The breasts were involuting. The posterior metastasis was completely excised, and a small fragment was removed for microscopic examination from the right posterior edge of the anterior metastasis. This could not be satisfactorily excised without considerable danger of injury to the urethra. On the following day an X-ray of the chest failed to show any evidence of thoracic metastases.

On the forty-fifth day of the puerperium abdominal panhysterectomy was performed, with removal of both Fallopian tubes and ovaries. The uterus was 6.5 cm. long, and its greatest width was 5.5 cm. The endometrium was brown and wrinkled except for an area approximately 3.5 × 1.5 cm. at the fundus, where it was replaced by a mass projecting into the lumen. This mass was slightly papillary and consisted of a greyish-white slightly granular tissue at its base and covered with a layer up to 1 cm. thick of laminated, firm red blood-clot. The right ovary 2.5 × 1.5 cm., had a greyish-white cut surface except for a few small cysts up to 0.3 cm. in diameter containing watery fluid. The left ovary, 2.5 × 1.4 cm., contained a corpus luteum 1.2 cm. in diameter, 0.7 cm. thick and no content. The remainder of ovarian tissue was greyish-white and homogeneous. Histological examination showed chorion-epithelioma in both metastases, in the tissue removed from the uterus and also infiltrating the uterus at the fundus.

On the seventh day after operation clinical examination



FORTY-FIRST DAY AFTER DELIVERY

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showed that the anterior metastasis had undergone spontaneous resolution to about one-third of its original size. Fourteen days after operation it had disappeared, but on palpation slight thickening about the size of a split pea was still apparent about the centre of its original site. Twenty-four days after operation evidence of its existence, either visible or palpable, could not be found.

Gonadotropic hormone assays were made during the pre-operative investigations and post-operative care of this patient and are summarized below.

GONADOTROPIC HORMONE ASSAYS.

Time of Assay	Quantitative Aschheim-Zondek (3 c.c.)		Relation to clinical picture
	Positive	Negative	
After labour			
38th day	1/1000 (Friedman 20 c.c. 1/200)	1/1500	Pre-operative
45th day	—	—	Panhysterectomy. Posterior metastasis excised 4 days previously
Post-operative			
1 week	1/25	1/200	Anterior metastasis one-third original size
2 weeks	1/25	1/50	Anterior metastasis invisible, palpable, size of split-pea
3 weeks	1/1	1/50	Anterior metastasis invisible and impalpable
4 weeks	1/1	1/10	
6 weeks	1/1	1/10	
9 weeks	—	1/1	

Monthly assays to date (13 months post-operative) have remained consistently negative 1/1.

The positive Aschheim-Zondek assay 1/1000 dilution with a total of 3 c.c. of urine injected is equivalent to the presence of 333,000 mouse units per litre of urine.

In conclusion, I suggest that this survey of hydatidiform mole and chorion-epithelioma supports Blair-Bell's view that the aetiology of cancer is wrapped up in the biology of the individual, that is, it supports the cell autonomy theory as opposed to the parasitic theory.

Blair-Bell inclined towards the view that chorion-epithelioma was a simple hyperplasia of a normally malignant tissue. It is a unique growth in that it is neither a true malignant growth of the cells of one individual nor is it a true implantation from a different individual. It is spontaneously cured more often than any other known malignant neoplasm, and yet, when resistance to its spread is broken down it runs a more rapidly fatal course than any other neoplasm.

It is curious that although Blair-Bell thought to cure cancer by means of agents which control or destroy the growth of chorionic epithelium he never published a case in which he had applied his remedy to the treatment of chorion-epithelioma.

The solution to the problems presented by the aetiology of cancer may be simplified by further investigation of the chorionic epithelium in both its benign and malignant forms.

Since the completion of this paper Mr. Alan Brews has communicated the following note regarding the frequency of vaginal metastases in a series of cases of chorion-epithelioma from 1885 to 1937. "Of the 24 female cases 14 came to post-mortem and in 7 of these there were vaginal metastases. In addition, a vaginal metastasis was recognized in one patient who survived; it underwent spontaneous resolution." This represents an all-over percentage of 29 and, if only the cases coming to post-mortem are considered, the percentage is 50 so that in this series the incidence of vaginal involvement is high.

REFERENCES.

1. Jeffcoate. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1938, xlv, 893.
2. Adams. "Genuine Works of Hippocrates" (London, 1849).
3. "History of Ancient Gynaecology." W. J. Stewart McKay, 1901, 194.
4. "Obstetric Medicine and Surgery." F. H. Ramsbotham (2nd edition, 1844), appendix L, 717.
5. "A Collection of Cases and Observations in Midwifery" (3rd edition, 1754), 98.
6. Madame Boivin. "Origin and Treatment of Vesicular Mole" (Paris, 1827).
7. Collected Works, ii (Frankfort, 1856).

8. Stacey, J. E. North of England Obstetric and Gynaecological Society. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1931, xxxviii, 471.
9. Winter, E. W. *Archiv. f. Gynäkol*, clv, 1933-34.
10. Fels. *Zentralb. f. Gynäkol. S.*, 466.
11. Ehrhart, K. *Surg. Gynaecol. and Obstet.*, 1931, liii, 486.
12. Roessler, H. *Monatsschr. f. Geburtsh. und Gynäkol.*, 1929, xcvi, 516.
13. Zondek, B. "Endokrinologie," v (Biedl. Festschrift, Leipsig, J. A. Barth).
14. Meyer, A. W. *Amer. Journ. Obstet. and Gynecol.*, 1918, lxxviii, 641.
15. Das, P. C. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1938, 265.
16. Essen-Möller. "Studien uber die Blasenmole" (Wiesbaden, 1912).
17. Blair-Bell, W. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1924, xxxi, 276.
18. Wilson, J. St. George. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1924, xxxi, 278.
19. Briggs, H. *Proc. Roy. Soc. Med.* 1912, v, 172.
20. Zondek, B. *Zentralb. f. Gynäkol.*, liv, 2306.
21. Boycott, M. Communicated from Obstetric Unit, University College Hospital.
22. Mathieu, A. *Surgery, Gynaecology and Obstetrics, January*, 1939, 52.
23. Sherman, J. T. *Amer. Journ. Surg.*, February, 1935, 237.
24. Lumsden, T. *Amer. Journ. of Cancer*, 1937, xxxi, 430.
25. Schlagenhauffer, F. R. *Wien. klin. Wochenschr.*, 1902, xv, 570 and 604.

Double Monsters in the Light of Recent Biological Experiments and Investigations regarding Heredity. Contribution to the Problem of the Determination of Sex

BY

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HUMAN double monsters are of very great interest to the student of heredity, as well as to the biologist, embryologist, and practitioner of medicine, but owing to their great rarity, about 1 in 50,000 births, the opportunities for their close investigation are very remote. The following 2 cases of double monsters observed in the Debrecen University Obstetrical and Gynaecological Clinic are, however, of exceptional interest because, apart from their general morphological peculiarities, one of the monsters showed a feature of unique interest in that one of its components was female, and the other externally a male, but shown on dissection to be a feminine pseudohermaphrodite.

Human double monsters have been repeatedly discussed from various view points, but they still afford a wide scope for research. In particular, their genesis is awaiting elucidation. This in turn would furnish a clue to several other problems in connexion with heredity and genetics. The biological experiments of Spemann[1] and of Mangold[2] throw some light upon the mode of embryogenesis of human twins and double monsters, and our cases have been studied from the point of view of Mangold's recent results.

REPORT OF CASES

CASE 1 (No. 1884/1937). Symmetrical monster (thoracopagus). Delivery having come to a standstill, after the rupture of the membranes and the birth of the head of one of the foetûs, the mother was brought to the clinic by her doctor. The foetal heart having stopped, delivery of the monster was effected by evisceration.

The parents were healthy and had 3 healthy children, 2 of whom were twins of the same sex, probably monozygotic.

Case 1. Fig. 1.

Case 1. Fig. 2.

Case 2. Fig. 3.

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The full-time thoracopagus foetûs were 45 cm. long, and had a combined weight of 5,600 grammes; their cranial circumferences were 33 cm. and 35 cm. respectively. They were facing each other and were united from the first rib to the origin of the umbilical cord (Fig. 1), as if they had been slit open along the sternum and their chests drawn asunder and allowed to hinge on the edges of corresponding sternal parts (Figs. 1 and 2). The right foetus had normal female external genitals; the left one, however, had a normal penis, 2 cm. long, with urethra and rudimentary scrotum (Fig. 2). Testicles were not palpable in the latter. The left foetus had also atresia ani; the right foetus, however, had a normal anus.

The placenta, umbilical cord, heart and liver were common. The cord had one vein and two arteries. The heart consisted of two halves. The right half (one auricle and one ventricle) supplied the right foetus, and the left half, also with one auricle and one ventricle, supplied the left foetus. The aortic arches and the great blood-vessels were situated as mirror images of each other. There were two pairs of venae cavae (superior and inferior), each pair opening into the auricle of the corresponding side. Both inferior venae cavae, however, received blood from the common liver. All other organs, viscera, the nervous system, and skeleton, were perfectly duplicated and formed mirror images of each other, with *situs inversus* in the right foetus (lungs, stomach, spleen, appendix). The internal genitals, however, were different. The right (female) foetus had morphologically a normal uterus, ovaries and Fallopian tubes. The bladder sigmoid, rectum and anus were morphologically normal. The left (apparently male) foetus had atresia ani and a rectum dilated to the size of an egg (megarectum). In the front of this there was a rudimentary uterus, the right corner of which was connected with a hypoplastic Fallopian tube and ovary. The uterus ended blindly between the bladder and rectum. A prostate was not found. All the 4 genital glands—including those of the apparent male—showed the structure typical of the ovary. The ovaries of neither foetus, however, had reached the stage of development normal in newborn infants. Especially undeveloped was the gonad of the hermaphrodite. Its external third consisted of purely tubular glands, either of ovarian vesicles or of tubules of the suppressed Wolffian body. In these epithelial canals there were a few scattered ova, as if the epithelium of the follicles was formed round the ova from the cells of the tubules. The 4 suprarenals had well developed cortical and medullary substances, with numerous fuchsinophil cells with abundant protoplasm and heaps of cells in the fasciculate and reticular zones, similar to those found by Broster and Vines[3] in connexion with pseudohermaphroditism and adolescent virilism in women.

Summary of the Morphological Peculiarities of Biological and Genetic Interest.

1. The right foetus was a normal female; the left foetus was a pseudohermaphrodite.

2. The left foetus had other developmental abnormalities, atresia and megarectum, which were not found in the right foetus.

3. The foetûs were united parallel to their longitudinal axis; their organs were mirror images of each other, with *situs inversus* in the right foetus.

CASE 2 (Old material from Clinical Museum). Symmetrical thoracopagus, delivered uninjured at 7 months. Both female. Details of delivery and history unknown. Union similar to that in Case 1 (Fig. 3). Head, skeleton and spinal cord were doubled. Placenta, umbilical cord (with one vein and two arteries), liver and heart were common. Other viscera were double and in mirror image positions with *situs inversus* in the right foetus. The following table gives the situations of the homologous organs:

Organs	Right foetus	Left foetus
Lungs	Right, 2 lobes; left, 3 lobes	Right, 3 lobes; left, 2 lobes
Stomach	Beside right kidney	Beside left kidney
Spleen	Right, beside stomach	Left, beside stomach
Appendix	Left, near liver and kidney	Right, near liver and right kidney
Aortic Arch	Bending to right	Bending to left

The neighbouring lungs (right lung of left foetus and left lung of right foetus), showed spongy, or honeycombed degeneration (congenital bronchiectasis. The spleen of each was hypoplastic, the size of a pea. The genitals of the left foetus were those of a normal female; those of the right foetus showed right hemiaplasia: only the left ovary and Fallopian tube and left half of the uterus being present. The single heart consisted of 2 ventricles and one auricle, but the great vessels: aorta, pulmonary artery and superior and inferior venae cavae were duplicated. The aorta and pulmonary artery of the right foetus came from the right ventricle, dextrofrontally; those of the left foetus, from the sinistro-posterior part of the left ventricle. The single auricle communicated with both ventricles (which had a wide interventricular foramen) by means of a common auriculo-ventricular foramen.

In this thoracopagus also, apart from the cutaneous, muscular and bony union, there was also intimate cardio-vascular, hepatic as well as placental circulatory union between the two foetûs.

Summary of the Morphological Peculiarities of Biological and Genetic Interest.

1. Right haemiaplasia of internal genitals in right foetus; those in the left being normal.

2. *Situs inversus* in right foetus.

3. Mirror image hypoplasia of lungs and spleen.

Discussion.

A highly important question in connexion with double monsters is their embryogenesis. The solution of this problem is intimately connected with matters of great genetic interest. The following modes of their genesis are theoretically possible:

1. As the result of some peculiarity of the male or female gamete. (a) A single ovum fertilized by a double-headed spermatozoon, or (b) a binucleate ovum fertilized, or caused to differentiate, by two or more sperms. In either (a), or (b), two embryonic *anlagen* will be formed, which, owing to the cohesion of the common pellucid zone, will unite in the chemically as yet indifferent neighbouring parts during the early cell division, possibly up to the time of gastrulation.

2. As the result of abnormal fertilization. (a) One ovum fertilized by two spermatozoa. (b) An over-ripe ovum which has divided immediately before fertilization, and the resulting two daughter cells became fertilized by two separate spermatozoa, or (c) After the division of an over-ripe ovum, one of the daughter-cells became fertilized and thus stimulated the other cell to develop parthenogenetically.

3. As the result of the abnormal differentiation of a normally fertilized single ovum, or of two normally fertilized ova. (a) The fusion of the *anlagen* of two separate developing ova at their neighbouring parts, in the chemically indifferent stage preceding gastrulation. According to Fischel,[4] this is the most frequent mode of genesis of human double monsters. He believes a full union to be prevented by some interposing cell mass. Double monsters arising in the manner described under 1, 2, and 3 (a), are binovular twins, and their components may differ in many respects, including sex. (b) The division of one zygote into two parts which differentiate independently of each other to a trophoembryoblast, but grow side by side owing to the influence of the pellucid zone, the neighbouring parts uniting in the chemically indifferent period before gastrulation (see later), or (c) the development of two incompletely separated *anlagen* from the embryoblast; the incomplete separation being due to some intervening obstacle, such as an interposing cell mass (Fischel). Monsters under 3 (b) and 3 (c), are like uniovular twins, very similar in all respects, and always belong to the same sex.

The following are the biological experiments and observations upon which the above theoretical speculations are based.

Binucleate ova occur in invertebrates and vertebrates alike. They also occur in man, though most uncommonly. In our

clinic we found 6 cases of binucleate ova in ripening and primordial Graafian follicles, among 500 adult women whose ovaries were for some reason removed. Double-headed spermatozoa have also been found, though uncommonly, in man (Broman,[5] and Stiasny[6]). Unfortunately, we know nothing of the ability of such spermatozoa to fertilize, or of such ova to be fertilized in man. Fol[7] and Hertwig,[8] experimenting on invertebrates, succeeded in inducing several spermatozoa to enter the same ovum, by means of chemical and physical agencies, such as chloroform or shaking.

A binucleate ovum 1 (b), or a double ovum 2 (b) and 2 (c) may begin to differentiate under the influence of a single spermatozoon, as the result of the activation of the unfertilized ovum or nucleus by the differentiating potency of the fertilized one. Such parthenogenetic development has been accomplished experimentally in the case of certain invertebrate ova by means of chemical or physical stimuli. Ova of frogs pricked by glass needles dipped in blood developed into mature frogs which were in all respects similar to normal ones, except that they were always of the same sex (females).

Fusion of various zygotes, even of zygotes belonging to different species, was experimentally achieved by Mangold on amphibian (triton) ova, at the time of the first divisions. It depended on the further manner of the segmentation of the cell-group thus produced, i.e., according as they split longitudinally, parallel to the animovegetative axis, or perpendicularly thereto, whether the further development resulted in one giant embryo or in a double monster. Spemann succeeded in producing experimentally from the triton ova twins or double monsters, in various forms at will, by suitably bisecting them in the time between the first segmentation and gastrulation. These experiments support the genetical hypothesis suggested under 3 (a) and 3 (b). At a later stage of segmentation, for example, after the formation of the neurula, these experiments are no longer successful, probably owing to the complicated differentiation and disharmony of the various cell-groups of the ovum, occurring at this time with the separation of the organ systems (phase of the chemical differentiation of the ova (Huxley,[9] and Huzella[10]). Spemann produced double monsters by compressing salamander ova longitudinally with the aid of a hair. If this compression reached the *anlagen* of the heart and stomach, the two resulting foetûs became stereoisomeric with *situs inversus* in the right foetus.

In human uniovular twins, stereoisomerism with *situs inversus* in one of the pair is occasionally found, though this is the exception rather than the rule. In double monsters, however, the incidence of *situs inversus* in the right component is fairly high, especially in thoracopagi, a phenomenon which can be biologically explained as follows:

The sinistral symmetry is probably determined by means of specific chemical substances in small groups of cells on the left side of the blastopore (in the early stages of blastula or gastrulation). If the embryonic *anlage* is bisected at this time, the right part remains without the portion directing symmetry. The symmetry of that part will, therefore, be accidentally determined by its position on the right side. Each of our two stereoisomeric thoracopagi can, therefore, be taken as derived from a single zygote at the stage of blastula or early gastrulation, when the centre governing symmetry had already been formed. In Case 2 the mirror-image positions of the developmental abnormalities in the lungs, congenital bronchiectasis, and the spleen, hypoplasia, is further proof of its monozygotic origin. The relative infrequency of stereoisomerism in identical, monozygotic twins, is difficult to explain on the basis of the biological experiments. Indeed, it would seem that *situs inversus* may be due to different factors in different circumstances, and when it occurs separately and not as a stereoisomerism, it is a Mendelian recessive, as shown by Feldman.[11]

Further evidence in favour of the uniovular origin of our cases is afforded by the following facts:—

1. Union occurred at homologous parts, viz. the chest, liver, heart, umbilical cord, placenta and placental circulation (St. Hilaire's law).

2. The longitudinal axes of both foetûs are parallel. It is easier to conceive that binovular double monsters will unite irregularly as regards their longitudinal axes, or by non-homologous parts.

According to Spemann a single zygote will develop into two complete foetûs, separate or conjoined twins, only if the split occurs parallel to the chief axis; the physiological apicobasal or vegetative axis (Child[12]), vertically dividing the *anlage* into right and left halves. Equatorial splitting will produce a complete foetus from the dorsal part, or animal pole, of the zygote, and a merely shapeless mass from the ventral part, or vegetative pole. This may also be the genesis of shapeless human monsters.

In invertebrates the poles are determined by the localization of the vitellum. In vertebrates, including man, it is supposed that the part of the ovum left more free during the process of ripening, which thus received a more plentiful supply of oxygen and food, will have a greater vitality and form the animal pole.

We can, therefore, explain the genesis of the monsters in both of our cases by the vertical division in the capitocaudal direction of a common embryonal *anlage*. The split which parted it into two, or directed its differentiation into two parts, started dorsally from the medullary lamina of the ectoderm and did not quite penetrate to the abdominal surface. The lower part of the entoderm, the liver, heart, and placental circulation remained undivided together with the placenta and umbilical cord, while the other organs and the two ends of the embryo developed into complete individuals. The union by the liver, and umbilical, and placental circulation would point to the division of the embryonal *anlage* at the time when the *anlagen* for the heart and vascular system were already differentiated, or when the primordial vitelline circulation was already formed. This is, of course, debatable.

Assuming now the monozygotic origin of our 2 cases, the question arises, what interpretation can be found for the differences in the genital organs, development, and character of the stereoisomeric foetûs, and how can these differences be brought into harmony with the laws of genetics governing monozygotic twins? The human double monsters hitherto described were all identical as regards the sex of each pair. Some authors consider this fact, in addition to the compliance with St. Hilaire's law, the strongest proof of their monozygotic origin. Only Feldman, in 1937, records that Dr. E. K. Hughes,[13] of Armidale, New South Wales, delivered in 1927, a woman, in the presence of two other doctors, of a stillborn 6 months' double monster; one foetus of which was male and the other female. The internal organs of the monster were, however, not examined, so that the sex of each of the foetûs remains doubtful. Our Case 1, therefore, which is the only one in the literature in which a human double monster, showing apparent heterosexuality, was shown on internal and histological examination not really to differ in sex, one foetus being a normal female and the other a feminine pseudo-hermaphrodite, may claim universal interest. The pseudo-hermaphroditism of one foetus need not signify a binovular origin, especially in view of other circumstances proving a uniovular origin; the mirror image position of the viscera, their

identical forms. The disturbance of the genital development suggests a more plausible explanation.

The occurrence of both sexes in one individual is physiological in numerous plants. Among animals it also occurs as an abnormality; often in lower animals such as ants, fruit flies, and poultry, but less often in higher animals. In man, too, different forms of genital aberration are known: hermaphroditism, intersex and different genital developmental disturbances. It is only in the last few years that attempts have been made to form a comprehensive theory of these on a basis of biological experiments and observations made by Goldschmidt,[14] Kovács,[15] Ludwig-Ries,[16] Moskowitz,[17] Mathes.[18] The foundations of a new theoretical conception were laid by Goldschmidt, who succeeded in experimentally producing analogues of the different genital developmental disturbances, such as double-sexed and intersexed individuals, sexual aberrations of man and animals, by crossing Japanese and European *Lymantia dispar*, a genus of butterflies.

All the above various observations teach us that every zygote has both male and female potentialities. Normally, the tendency for development into one particular sex is more pronounced and the zygote becomes a person of that sex. Its potentiality, however, to develop into the other sex lies dormant within it. During development and, indeed, throughout life, various factors cooperate to help the one particular sex to predominate in that individual. This predominance in higher animals depends primarily on the number of sex chromosomes in the zygote. This, in turn, depends on the fertilizing spermatozoon, whether it contains an X-chromosome or a Y-chromosome (Huxley). All ova contain an X-chromosome. An ovum fertilized by a spermatozoon containing an X-chromosome results in a zygote containing 2 X-chromosomes, and develops into a female; one fertilized by a spermatozoon containing a Y-chromosome results in a zygote having one X-chromosome and one Y-chromosome, and develops into a male. The hormonal system: suprarenals, hypophysis, and gonads, directed by these chromosomes, start functioning and produce the corresponding sex characters.

The working of the sex chromosomes may be disturbed at any time before or after birth, and consequently the development of sexual characters and sex organs can also be disturbed at any time. Wrong combinations of male and female genes may, according to Goldschmidt, occur at the time of fertilization. The difference between their potencies (epistasis, differences between male and female factors), is not great enough to determine the

organism firmly in one or other sex direction, but will decrease the sharp definition of the sexes. Depending on the difference between the male and female factors, intermediate sex characters (intersex), a mixing of male and female genitals (hermaphroditism), or different morphological and biological disturbances of the genital organs will arise, for example, absence of gonads, or precocious puberty. Even already developed genitalia may regress and genitals of the other sex develop in their stead. The cause of these sexual aberrations lies in hereditary as well as in environmental factors. Kovács succeeded in controlling the sex of embryos by injecting testicular extracts into female rats, while Ludwig-Ries attempted the same with progynon in the case of chick embryos. Suprarenal tumours may alter the secondary sex characters of their hosts, as seen in cases of different forms of interrenalism: precocious puberty, heterosexual changes, hirsutism, virilism and pseudo-hermaphroditism. According to Broster and Vines, the persistence of certain cell groups usually present only in the embryonic phase in the suprarenal cortex, and according to Törö,[19] the retarded involution of the Wolffian bodies, and possibly some other, at present unknown, factors, have a similar effect.

I have described cases from our hospital of the persistence of the Wolffian body in the ovaries of women with aplasia of the genitals. The *rôle* of the suprarenal cortex in certain anomalies of sexual development such as precocious puberty, and virilism in post-natal life is no longer disputed. Kovács described a case of virilism in a woman without a suprarenal tumour. The sexual transformation, characteristic hirsutism, occurred in a woman 48 years old, after double ovariotomy. The role of a functional or neoplastic affection of the suprarenals in causing pre-natal pseudo-hermaphroditism has not yet been established. Several cases of external feminine pseudo-hermaphroditism, with suprarenal hyperplasia or tumour have been described (Kraus[20]), but these were considered by some as merely co-ordinated disturbances, and not the cause of the hermaphroditism. Goldschmidt and others, however, consider these cases as examples of innate virilism. Apert[21] belives the changing periodicity of sexual functions to account for the different influences of suprarenal tumours; prenatally the organism reacts to the increased influence of the suprarenal cortex, by pseudo-hermaphroditism; before puberty, by precocious puberty; at the time of sexual involution, by virilism.

Broster and Vines found fuchsinophil cells in the suprarenal

cortex of hermaphrodites and virile women. These cells have a masculinizing influence, but their hormone is not identical with androsterone. These cells are present in every foetus from the ninth to the seventeenth weeks. They appear earlier, and in greater amounts in males and disappear earlier in females, viz., at the time of the involution of the Wolffian bodies. Broster and Vines, therefore, attribute hermaphroditism and virilism to the persistence of these fuchsinophil cells.

If mixed sex can appear in one individual, it may also occur in monozygotic twins and double monsters, even though an instance of this has not yet been described. It is very difficult to say why in our Case 1 only one half of the zygote became hermaphroditic although both components contained the same sex endowment. We have found fuchsinophil cells in the fasciculate and reticular zones of the well-developed cortical part of the suprarenals of both foetûs. Remnants of the Wolffian body or imperfect testicular tubes were also found in the ovaries of the hermaphrodite. We doubt if the developmental disturbance of the anus was influenced by the genital disturbance.

We may therefore maintain that our double monsters came from single zygotes, probably in the way described under 3 (b). The hermaphroditism and atresia ani only in one of the components in Case 1, and the hemiplasia of the internal genitals of only one component in Case 2, is no proof of the monsters' not being monozygotic. Litte Straus,[22] Steiner,[23] Bololi,[24] and especially Szendi,[25] emphasized the possibility of there being exceptions to the anthropological and hereditary rules in connexion with monozygotic twins. But the explanation of these exceptions so as to make them agree with the laws of heredity is rather speculative even if it utilizes the result of researches on drosophila genes. Verschuer,[26] for instance, believes that in such cases one half of the zygote does not remain vital enough to develop completely, while Cockayne (quoted by Feldman), would suppose that the dominant gene for hermaphroditism fails to enter that half of the zygote which became a normal female.

But there is another disturbing factor in connexion with the stereoisomerism of all double monsters. In the case of monozygotic twins there is a particular similarity in the finger-prints of the corresponding fingers of opposite hands. The finger-prints of the components of double monsters, however, show very little similarity. Indeed, in the case of the surgically separated Nigerian xiphipagous twins, the finger-prints investigated by Feldman (private communication to the author), did not show any homo-

lateral or heterolateral similarity in the patterns of the tips of corresponding fingers.

Summary.

Two thoracopagi were studied. The union in each pair was by homologous organs parallel to their longitudinal axes. They were stereoisomeric as regards their morphology and pathological changes in their organs. The genital organs, however, were differently developed in the two members in each pair. One member of the first pair was a hermaphrodite and one member of the second pair had hemiplasia of the genital tract. It would appear, however, from recent research in the biology of sex as well as of uniovular twins, that such differences may also occur in two individuals derived from the same zygote. These double monsters are, therefore, to be regarded as monozygotic in spite of these differences. The pseudo-hermaphroditism may possibly be due to the persistence of the fuchsinophil masculinizing cells in the suprarenals, although if this be the case it is difficult to see why the other foetus which also had these cells should have escaped hermaphroditism. The mechanism of these cells and of the Wolffian body's persisting in the ovaries, the way they act on sex chromosomes to transform sex, as well as the interpretation of the genital hemiplasia in one of the foetûs in Case 2, will only be elucidated by future research.

References.

1. Spemann. "Theorie d. Entwicklung." Berlin, 1936; *Zool. Zb.*, Suppl. 7, Festchr. f. A. Weismann. S. 429-470, 1904b.
2. Mangold. *Arch. Entw. mechan. der. Org.*, 1920, xlvii, 248–301. *Ergben. Biologie*, Bd. 3, 5, 7. Extrait des comptes Rendus du XII Congr. Zoologie, Lisbon, 1935.
3. Broster, L. R., and H. W. C. Vines. "The Adrenal Cortex," London, 1933. *Brit. Med. Journ.*, 1937, 1, 662.
4. Fischel. "Entwicklung des Menschen," 1929. Vienna and Berlin. J. Springe.
5. Broman. Quoted by Fischel.[4]
6. Stiasny. *Zentralb. f. Gynäkol.*, 1937, 15.
7. Fol.
8. Hertwig.
9. Huxley, Julian. "Problems in Experimental Embryology," Cambridge, 1934. "Reproduction, Heredity, and the Development of Sex," London. "Essay in Popular Science and Essay of a Biologist," London.
10. Huzella. "Az élet tudománya," Franklin, Budapest.

11. Feldman, W. M. *The British Encyclopaedia of Med. Practice*, Vol. I, 1937, 5, pp. 334–387.
Feldman, W. M. *Proc. Roy. Soc. Med.*, London, 1935, xxviii, 753.
12. Child. Quoted by Huxley.
13. Hughes, E. K. Quoted by Feldman.
14. Goldschmidt. W. Stoeckel's *Handbuch Gynäkol.*, Bd. ix, Munich, 1936.
15. Kovács, F. *Amer. Journ. Obstet.*, 1925, 4.
16. Ludwig-Ries. *Zentralb. f. Gynäkol.*, 1936, 33; 1938, 43.
17. Moskowitz. *Arch. f. Gynäkol.*, Bd. 11, H. 1, 2.
18. Mathes. Quoted by Moskwitz.
19. Törö. *Anat. Anzeiger*, Bd. 82.
20. Kraus, E. J. W. Stoeckel's *Handbuch Gynäkol.*, Bd. iv, Munich, 1936.
21. Apert. W. Stoeckel's *Handbuch Gynäkol.*, Bd. ix, Munich, 1936.
22. Litte Straus. *Amer. Journ. Obstet.*
23. Steiner. *Arch. f. Gynäkol.*, Bd. 156.
24. Bololi. *Benichte Gynäkol.*, 33.
25. Szendi. *Zentralb. f. Gynäkol.*, 1937, 21, *Arch. f. Gynäkol.*, Bd 165. H. 3.
26. Verschuer-Diehl. "Zwillingstuberculose," Jena, 1933.

Vaginal Hysterectomy

A New Technique. A follow-up of 500 Consecutive Operations for Haemorrhage

BY

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Vaginal hysterectomy is one of the oldest of operations. Paul of Aegina (625–696) advocated it for irreducible inversion; Albucasis the Arabian (1073–1106) advised it for ulcerated prolapse. It is not mentioned during the Renaissance, nor is there any evidence that Ambrose Paré practised it. It was not till 1818 that the first monograph on the subject was published by Lagenbeck, his lead being followed in 1822 by Sauter who described a technique for the removal of a carcinomatous uterus.

In 1878 Freund[1] popularized the operation by a technique which was adopted by the whole surgical world—a technique which is still practised with small modifications by some, but to-day such a method cannot be accepted as sound for it leaves the vault of the vagina gaping, which, apart from the risk of sepsis, carries with it the immediate danger of obstruction from descent of a loop of bowel, and the subsequent disability of cystocele and possibly enterocele.

Doyen (1859–1916), that quaint and entertaining creature, whom many a time I have heard declaim " no man can call himself a gynaecologist until he can perform a vaginal hysterectomy in private ", did much to encourage the operation by the use of clamps. However, despite his nicety of judgment, and digital skill in all surgical work, he was insistent on the fact, as others are to-day, that circumstances do arise which indubitably call for the removal of the uterus only through the vagina, conditions that demand imperatively that the gynaecologist shall be capable of applying as faultless a technique *per vaginam* as he would if performing *per abdomen*.

But since the days of Doyen, although Continental and American surgeons have published countless and beautifully illustrated papers, little has been done in this country; indeed, from 1902 to 1939 only 16 British surgeons have recorded cases in the *British Journal of Obstetrics and Gynaecology*, and not one of these describes or depicts the method used; similarly on referring to the *Proceedings of the Royal Society of Medicine*, I find that on one occasion only was vaginal hysterectomy a subject for discussion during the last 24 years.

That this operation is not popular in many clinics of the Empire is remarkable, for there can be no question that it is accompanied by less shock, the convalescence is more rapid, the administrative cost is less, and that the mortality is lower than the abdominal route. Moreover, apart from the minor fact that there cannot be any hernia or scar, there is the advantage that any laxity or prolapse of the vaginal walls can be dealt with at the same time.

Admittedly radium has its greatest use for carcinoma, but it is doubtful whether it is as valuable for many cases of haemorrhage as vaginal hysterectomy, for apart from its cost, radium destroys healthy ovaries to conserve a potentially dangerous uterus, and is followed by far more distressing menopausal symptoms.

During 1938 I had the privilege of being President of Honour of the French Gynaecological Society. While in office I was asked to demonstrate the method of vaginal hysterectomy which I have evolved and used for 10 years in a consecutive series of 500 cases for uterine haemorrhage.

At two séances I had the good fortune to be attended by Dr. Raoul Palmer, Gynaecologist to the Broca Hospital in Paris. I am indebted to him for the excellent pen and ink drawings which fill the gaps in the accompanying description of an operation which removes the uterus, counters any subsequent tendency to cystocele or enterocele and is based on sound tactical principles.

1. After thorough cleansing of the parts with dettol and dettol cream, the labia are stitched back laterally by two sutures.

2. The cervix is closed by three stout silk sutures which are left long to act as retractors. (Fig. 1.)

3. An injection of 2 c.c. pituitrin is made into the paracervical tissue and a catheter is passed.

4. A circular incision is made round the cervix, and with the handle of the knife the mucous membrane is firmly deflected upwards. This is important lest later the sutures embrace the edges and so cause local sloughs. If there is any cystocele the incision should start three-quarters of an inch from the urethra and be

carried down the anterior wall of the vagina to the cervix whence it is continued transversely in a ⊥ form round the cervix. If desired this incision can be made with a diathermy cutting knife to stop oozing from the edges.

5. The pouch of Douglas is now opened. (Fig. 2.) Two fingers are then introduced to explore the back of the uterus and the adnexa. If any adhesions exist between the uterus and the bowel they can readily be separated.

6. Now, by cutting at a right-angle on to the cervix it is very easy to get into the plane of the vesico-vaginal fascia. With the handle of the knife or a gauze-covered finger, the bladder is then quickly elevated and the shining utero-vesical pouch of peritoneum seen.

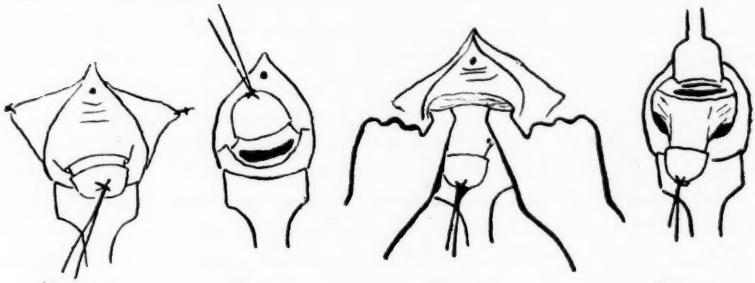

FIG. 1. FIG. 2. FIG. 3. FIG. 4.

FIG. 1. Circular incision.
FIG. 2. Pouch of Douglas opened.
FIG. 3. Deflecting Ureters.
FIG. 4. Utero-vesical pouch opened.

7. At this stage, *before opening the pouch*, the two index fingers are introduced under the bladder and the ureters on each side are pushed well away on each side. (Fig. 3.)

8. A flat retractor is placed under the bladder and the utero-vesical pouch of peritoneum is opened with scissors. (Fig. 4.)

9. With the left index finger in the pouch of Douglas and using a blunt Reverdin needle from before backwards, the tissue comprising the descending cervical artery and the uterosacral ligament is ligatured, using No. 3 catgut. (Fig. 5.) A knife is used then to divide these structures. The same procedure is followed on the other side.

One very important point of all ligatures at this and the next stage of the operation is that after the first knot is tied tightly, the

tissues are cut, this gives one the opportunity of still further tightening the first knot before tying the second and third knots, so that bleeding later is impossible.

10. With the left index finger still in position, the blunt needle then takes up the uterine artery where it approaches and ascends the lateral wall of the uterus. (Fig. 6.) This ligature is made to overlap the previous ligature mentioned under heading 9, so that there can not be any possibility of slipping. After the first knot has been tied firmly the cardinal ligament enclosing the artery is cut and the second and third knots are tied. When these tactics have been followed on the other side it is pleasing to see how the uterus descends when the cardinal ligaments have been divided. The whole field is now perfectly dry.

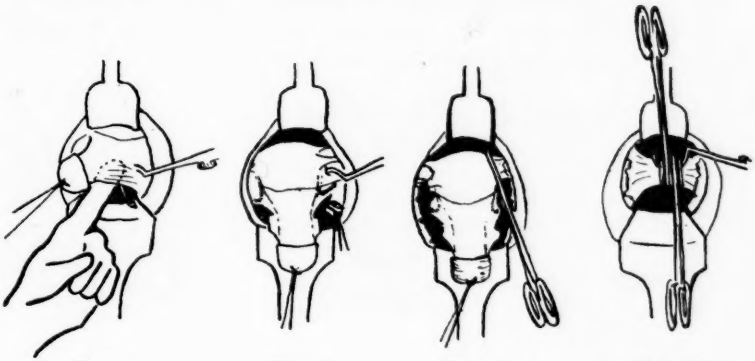

FIG. 5. FIG. 6. FIG. 7. FIG. 8.

FIG. 5. Descendens cervicis artery and utero-sacral ligament ligated.
FIG. 6. Ligation of the uterine artery.
FIG. 7. Clamping the top of the broad ligament.
FIG. 8. Apposing and suturing of the broad ligaments to form the bridge.

A third ligature may be applied at this stage to take up the anastomising uterine and round ligament arteries, or if preferred a further ligature of security can be placed on the uterine alone.

11. The uterus being now in full view a long forceps is placed to the top of one broad ligament, three-quarters of an inch from the uterus, comprising the tube, its mesosalpinx, and the round ligament. (Fig. 7.) With scissors the uterus is freed on that side. The same procedure is followed on the opposite side and the organ is delivered to the assistant to open.

The Fallopian tubes and ovaries are now inspected, if normal they are left, if morbid they are removed on one or both sides.

12. Now arrives the most important step in the operation from the point of view of the future, that is making the " bridge " which will prevent herniation of the bladder or bowel. We have seen that the cut surfaces of the broad ligaments are now aligned and facing outwards so that there is no risk of a loop of bowel becoming adherent to raw or non-peritonealized areas. (Fig. 8.) The apposed broad ligaments are now sewn together by three ligatures of stout catgut, the first comprises the upper portion of each, the second takes up the lower part and these two ligatures are left long, the middle suture is a mattress one taking up the centre of the ligaments. (Fig. 9.) It is with the upper and lower long ligatures that we are concerned since they (*a*) close the gap between the bladder and the top of the broad ligament, and (*b*) close the gap between the rectum and bottom of the broad ligament.

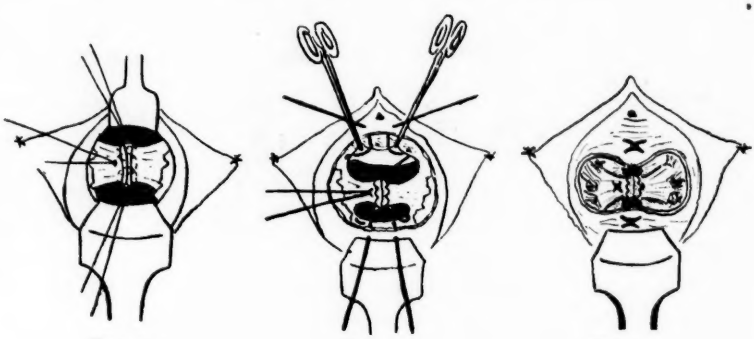

FIG. 9. FIG. 10. FIG. 11.

FIG. 9. The bridge formation.
FIG. 10. Method of counteracting cystocele or enterocele
FIG. 11. Sutures tied and bridge completed.

To achieve this, first it is necessary to bring down the fish-belly-like peritoneum of the utero-vesical pouch which has retracted high up, under and away from the bladder—this is quite easy with two long forceps which splay it out. (Fig. 10.) A sharp Reverdin needle is then introduced through the vaginal mucous membrane one inch from its anterior cut margin; it passes through the fish-belly-like flap of the peritoneum and then one long end of the bridge suture is picked up and withdrawn. The procedure is repeated with the other end and the two sutures are tied firmly so

that now the peritoneum below the bladder is closely adherent to the top of the broad ligament. (Fig. 11.)

For the posterior portion, the Reverdin needle is passed one inch from the cut hind wall of the vagina through it and the peritoneum on the floor of the pouch of Douglas. The lower long bridge suture is picked up and withdrawn and the opposite side treated similarly. (Fig. 10.) When these ligatures are drawn tight, the aperture between the rectum and the posterior margin of the broad ligament disappears. (Fig. 11.)

13. All catgut ends having been cut and complete haemostasis obtained, the edges of the vagina are apposed horizontally with separate sutures. (Fig. 12.) At one time I used to insert a rubber cigarette drain for 24 hours, but I have now given this up; if, however, the field gives the slightest suspicion of oozing it is a good plan.

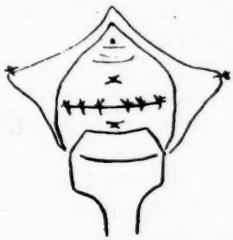

FIG. 12. Vaginal vault closed horizontally.

14. The vagina is stuffed with gauze soaked in paraffin and acriflavine and a self-retaining catheter is inserted. The gauze and catheter are removed after 48 hours.

COMMENT

The operation which has been described and depicted is well adapted for cases of haemorrhage or small fibromata. It counters certain defects of other methods for it leaves the floor of the pelvis firm and strong. Of this I have satisfied myself, for in a previous large series before I adopted this technique there was often subsequent bulging or giving of the vault and walls of the vagina. Gynaecologists here and abroad who have merely apposed the anterior flap of peritoneum to that of the pouch of Douglas (the usual technique) have also told me the same thing. The bridge formation is essential.

If there is any rectocele or cystocele it can be readily dealt with

at the same time or at a later date if preferred. Personally I have performed very few vaginal hysterectomies for complete prolapse (18 in all), preferring the Fothergill of Manchester or the Watkins of Chicago technique. The Ward Mayo operation is excellent, but I have found the combination of plastic vaginal surgery at one and the same sitting to be somewhat a formidable procedure in elderly frail people. I have never had to make a Schuchardt incision.

Thrice only have I during the last 10 years performed vaginal hysterectomy for cancer of the cervix; once was for a midwife who weighed 16 stone—she is still alive and working. Once for a patient suffering from Graves's disease. She died 6 years later. Once in a mother of 4 children who was 3 months pregnant with an early cauliflower carcinoma. She refused all other treatment, but 6 months later there were signs of recurrence and she died within a year.

I do not think vaginal hysterectomy should to-day be attempted for a tumour larger than a 12 weeks' pregnancy, or shall we say a cricket ball, and even then only if the genital aperture is sufficient.

A routine plastic repair operation can always be performed when necessary. In this series, on 47 patients it was done at once; on 28 at a later date.

Some surgeons advocate routine bisection of the uterus, but there are no advantages in this unless the uterus is fixed by old parametritis or is too large to come through entire. Morcellement of a fibroma is a disagreeable business, and unless done *tour de force*, is usually unwise.

Very rarely have I performed vaginal hysterectomy in a nullipara.

The whole technique takes, on an average, 35 minutes.

Complications

In these 500 cases twice have I had to open the abdomen after operation, once on the 3rd day for obstruction due to a loop of bowel adherent to blood in the pelvis; on another occasion 24 hours after operation the patient showed signs of intraperitoneal bleeding due to slipping of a ligature. Both recovered uneventfully. It was interesting in each case to see from above that the pelvic floor area was competely peritonealized and secure.

In no case has the ureter been injured. In one case the bladder was incised in opening the anterior pouch; it was immediately repaired with fine catgut and the operation proceeded with.

In one case a stone formed in the bladder a year later. In one

case, nine days after operation, a vesico-vaginal fistula formed. This was in an old lady of 65 in whom a previous diagnostic curettage had been done and the curettings reported innocent, but when the uterus was removed there was found to be carcinoma at the isthmus.

Mr. James Carver saw her with me and agreed that the fistula was of the type secondary to carcinoma which was not likely to heal, and so I implanted both ureters into the colon, using the technique I have previously described. She made an uneventful recovery but died 12 months later.

In another case, a woman was sent to hospital for haemorrhage. The uterus was the size of a 2 months' pregnancy and the cervix was horribly lacerated and eroded. Curettage showed nothing abnormal.

She returned, however, a month later bleeding excessively. A vaginal hysterectomy was performed. Eight days later, much to my dismay, she developed a recto-vaginal and a vesico-vaginal fistula. The whole vault of the vagina when exposed had the appearance of a large granuloma.

On account of this a Wassermann test was made which proved 100 per cent positive. On antisyphilitic treatment the fistulae closed in the course of 3 months.

In 3 cases a pelvic abscess was opened for an infected haematoma after a week of fever; in all of these diarrhoea and the passage of mucus *per rectum* indicated that there was irritation and pressure on the bowel. There was no case of secondary external haemorrhage.

CASES.

1.	Post-menopausal bleeding. Aetiology uncertain, i.e. Atrophic endometritis; fibrosis uteri	47
2.	Metropathia haemorrhagica and adenomyosis	156
3.	Polypi	54
4.	Fibromata	163
5.	Deep cervical laceration and erosion; or cystic hypertrophy of the cervix associated with irregular bleeding and first degree of prolapse	53
6.	Retroverted subinvoluted uterus (chronic metritis)	15
7.	Cancer of the cervix	3
8.	Chorion epithelioma	2
9.	Cancer of corpus uteri	7
	Total	500

Average age equals 44.1 years.

In the immediate after-treatment of these cases I believe a very important point is to keep the patient absolutely flat for 48 hours, encouraging her to take deep breaths and turn from side to side from the first, the reason being that if she is at once put in the semi-Fowler position a loop of bowel may fall down into the pelvis and become adherent, perhaps giving rise to obstructive symptoms.

Mortality

Total consecutive cases: 500. 6 deaths: 1.2 per cent.

One patient died of acute dilatation of the stomach proved at autopsy.

One died of tympanitic ileus without any definite cause such as inflammation or obstruction to be found post mortem.

Two died of acute septic peritonitis; in one of these, an elderly debilitated woman, a high colpo-perineorrhaphy completely sloughed and the infection spread upwards.

One died of embolism.

One died of broncho pneumonia.

Finally I wish to thank Miss A. Allen for her labour in checking the Hospital case sheets.

Bibliography.

Lagenbeck, C. J. M. "Biblioth f. d. Chir." (Hanover, 1818), Vol. i, p. 557.

Sauter, J. N. "Die Gänzliche Exstirpation des Carcinomatosen Geburmutter" (Constance, 1882).

Freund, W. A. Volkmann's "Sammlung Klin Vorträge" (1878), No. 133.

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Green-Armytage, V. B. *British Journ. of Surg.*, 1932, ii.

An Investigation of Cases of Recurrent Abortion and their Treatment with Progesterone

BY

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It is recognized that the preparation of the uterine endometrium and the process of implantation of the fertilized ovum are initially associated with the persistence of the corpus luteum of pregnancy. Abortion or absorption of foetûs can be induced in the experimental animal by the removal of the corpus luteum, but in the human it has been shown that pregnancy can continue to term after the removal of the corpus luteum in early pregnancy.[1] It has, therefore, been suggested that, in man, some other structure takes over the function of the corpus luteum, for pregnandiol, an end-product of progesterone metabolism, has been recovered from the urine after the corpus luteum has been removed. The placenta probably functions in this way,[1] and it may, therefore, be supposed that the corpus luteum itself is responsible for the embedding of the ovum and its nutrition in the early phase of pregnancy, but that later this role is, or can be, taken over by the functioning placenta. An active corpus luteum is dependent, in its turn, on the supply of an anterior pituitary hormone, and there is evidence of overfunction of the anterior pituitary in early pregnancy.

Evidently, failure of a pregnancy to continue to term would result from a deficiency of either or both of these hormones, but before it is possible to draw any conclusions from their amount in cases of recurrent abortion, it is obviously necessary to know the quantities secreted in normal pregnancy. It is not feasible at present to estimate the concentration of these hormones in the blood, and accordingly the concentration in the urine of the hormones themselves or their metabolic products has been

studied as a measure of their production. The hypophyseal hormone can only be determined biologically, and although the substance estimated during the earliest phase of pregnancy may be a true hypophyseal hormone, it seems likely that the chorionic epithelium elaborates a somewhat similar hormone. Progesterone, the corpus luteum hormone, is not excreted as such, but pregnandiol, which is probably its main breakdown product, can be recovered chemically from the urine, in which it appears chiefly as a diglucuronide.

Once knowledge of hormonal behaviour in normal pregnancy has been obtained, it becomes possible to inquire how far failure of the hormone control is responsible for abortion, and to study intelligently the possibility of preventing abortion by hormone therapy. Obviously, information on these points can best be obtained from a series of cases in which there is a reasonable expectation that pregnancy will, if untreated, end in abortion. Now the number of women with a history of one previous abortion is much greater than the number with two abortions, and as the number of successive abortions increases, the number of possible cases progressively decreases. It is, therefore, important to know what number of successive abortions may be taken as indicating the existence of some intrinsic defect which is preventing a pregnancy at term. Malpas[2] suggests 3 abortions as a minimum, showing that by the laws of probability it is highly unlikely that a sequence so long would be due to accidental causes of abortion. The figures given by Malpas strikingly support his view. There is, however, the possibility that a hormonal defect may occasionally be non-recurrent, and if such a defect appeared in one pregnancy but not in a subsequent one, it would be one of the accidental causes of Malpas. It is impossible, in fact, to say that hormonal deficiency as a cause of abortion is limited to those 1 per cent of pregnancies which fulfil Malpas's conditions for inclusion in the number of cases incapable of continuing pregnant to term.

For experimental purposes, however, it is obviously unfair to include in the series women with a history of only a single abortion, for in such cases the probability is high that the previous abortion was accidental. Ideally, the criterion of Malpas should be taken, and only those women included who have had a sequence of 3 abortions. In practice, we have been unable adhere to this ideal, and have investigated cases in which women have had two or more successive abortions, though admittedly, on the basis of Malpas's calculations, this does

increase the difficulty of interpreting the results of treatment. We suggest, however, that Malpas's estimate of the likelihood of recurrent abortion is rather low, and that his estimate of the likelihood of a successful pregnancy following a sequence of two abortions is consequently rather high.

Our Table I is abstracted from Malpas's Tables I and II, and gives the results of calculations which show a close correlation with the data on frequency of abortion collected by Whitehouse. Malpas suggests that the figures for the expected percentage of abortions, calculated on the assumption that a recurrent cause is operating in 1 out of 18 cases of abortion, correlate very well with the observations of Whitehouse. He points out, quite rightly, that close correlation cannot be expected in the cases of more than 3 successive abortions, since in practice one has to reckon with avoidance of pregnancy after a series of abortions. It seems to us, however, that the correlation between the calculated and the observed figures is, for women with up to 3 abortions, just as good if one assumes a recurrent cause in 2 out of 18 cases, and with this assumption the chances of a successful pregnancy following 3, or even 2, abortions are markedly reduced. Probably the truth lies somewhere between these extremes, and we are justified in believing that after 2 successive abortions the probability of abortion in a third pregnancy is about 50 per cent, that after 3 abortions the probability of abortion in the fourth pregnancy is about 80 per cent, and that the probability rises to over 90 per cent after

TABLE I.

No. of previous successive abortions.	Percentage chance of successive pregnancies.		No. of abortions per 100 women in successive pregnancies.		
			Expected		Observed*
	(*a*)	(*b*)	(*a*)	(*b*)	
0	82.00	82.00	18.00	18.00	18.0
1	78.40	74.70	3.89	4.56	4.3
2	62.00	47.00	1.48	2.41	2.1
3	27.00	14.60	1.08	2.06	0.7
4	6.00	3.00	1.01	2.01	0.6

(*a*) Assuming 1 abortion in 18 to be due to a recurrent cause.
(*b*) Assuming 2 abortions in 18 to be due to a recurrent cause.

* *From data given by Sir Beckwith Whitehouse.*

a sequence of 4 abortions. Thus, in a series of cases with at least 2 successive abortions, but including a number with 3, the expectation of abortion in the next pregnancy is about 65 per cent. This reduced expectation of abortion as compared with that in a series of cases with a succession of at least 3 abortions is, however, compensated for by the much greater number of cases available.

Methods of Investigation.

At first we treated empirically women with a sequence of two or more abortions, giving progesterone in small doses throughout the pregnancy and attempting to evaluate the results on a semi-statistical basis. Soon, however, we realized the practical impossibility of gauging the proper dose of progesterone without some knowledge of the amount normally produced and metabolized. Further, it seemed possible that estimations of the actual hormone production in the cases studied might give information as to which in fact were producing abnormally low amounts and which, therefore, might be expected to benefit from administration of the hormone. We therefore estimated the excretion of the gonadotropic hormone and of pregnandiol diglucuronide (representing progesterone) at short intervals during normal pregnancies and also in cases of recurrent abortion. In the latter group of cases, of course, the estimations were begun before treatment. An estimate of oestrogenic hormone excretion was not made. All estimations were made on 24-hour collections of urine, for the completeness and accuracy of which, however, we had to depend entirely on our patients, most of whom were living at home throughout the period of observation. It is possible that some irregularities in our figures may be due to collection errors. For the same reason, namely, that our subjects were out-patients, we were unable to make the estimations either as frequently or as regularly as we should have liked.

Pregnandiol was determined by the method of Venning,[3] which was found to work well, and does not need any description here. It should perhaps be mentioned that since this method depends upon the actual isolation of the pregnandiol derivative, the results are really minimal quantities present, and in particular, a negative result merely means that the amount present, if any, was too small to be isolated.

Since various methods exist for the estimation of the gonado-

tropic hormone, it is desirable that the one we used should be briefly described. The gonadotropic hormone was extracted from the urine by the alcohol precipitation method. An equal volume of alcohol was added to 150 cubic centimetres of the urine under test, and the mixture was centrifuged. The supernatant fluid was poured into 600 cubic centimetres of alcohol. (The alcohol used in these procedures was 95 per cent ethyl alcohol.) An hour later the liquid was centrifuged, and the precipitate, which contained the hormone, was suspended in 100 cubic centimetres of ether, separated again by centrifuging, and dried in a desiccator. The dry powder was dissolved in 60 cubic centimetres of distilled water for testing, and 10 cubic centimetres of this solution were diluted with 20 cubic centimetres of distilled water for a second test. The first solution, of which 3 cubic centimetres were equivalent to 7.5 cubic centimetres of urine, is referred to as "dilution 1/1", and the diluted solution, of which 3 cubic centimetres were equivalent to 2.5 cubic centimetres of urine, as "dilution 1/3". For testing each dilution, 10 immature female rats, weighing between 38 and 45 grammes, were used. Each rat received subcutaneously 1 cubic centimetre of the appropriate test solution daily for 3 days The rats were killed on the fifth day, and the ovaries were immediately dissected from their capsules and rapidly weighed on a torsion balance. For determining the increase in weight due to the hormone, we took 10 milligrams as the average weight of the ovaries of rats of the size and strain (Wistar) used, a figure which resulted from the examination of 40 control animals. A series of experiments with graded doses of a single preparation of gonadotropic hormone showed that for increases of ovarian weight up to 35 milligrams there was a roughly linear relation between amount of hormone and increase in ovarian weight. Beyond that, however, the response to increased dosage rapidly decreased. For assay purposes, therefore, we accepted the results using "dilution 1/1" only when the average increase in ovarian weight was less than 35 milligrams: when it exceeded that figure the results from the series with "dilution 1/3" were used. The unit was taken as the amount of gonadotropic hormone (i.e. the volume of urine) required to produce a 5 milligram increase in ovarian weight.

Both for pregnandiol and gonadotropic hormone, the daily output was calculated rather than the concentration per litre of urine.

Results and Discussion.

Excretion of Gonadotropic Hormone.

The quantitative excretion of gonadotropic hormone throughout pregnancy has been determined by several workers, and their results agree in indicating that there is a peak in the amount of hormone excreted daily during the early months of gestation. Thus Browne and Venning[4] found that the concentration of the hormone in the urine rises rapidly between the fortieth and the fiftieth day after the beginning of the last menstrual period, and reaches a maximum between the fiftieth and sixtieth days; this maximum is maintained for only a few days and is followed by a rapid fall in the concentration to a low and constant level which is maintained until parturition. The assays of the gonadotropic hormone excretion in our normal cases agree generally with these findings (Fig. 1) although we have not been able to determine the excretion of the hormone before the fifty-fifth day of pregnancy. We find, however, a tendency for the gonadotropic hormone excretion to increase somewhat in the later months of pregnancy, and thus to run parallel with the excretion of pregnandiol.

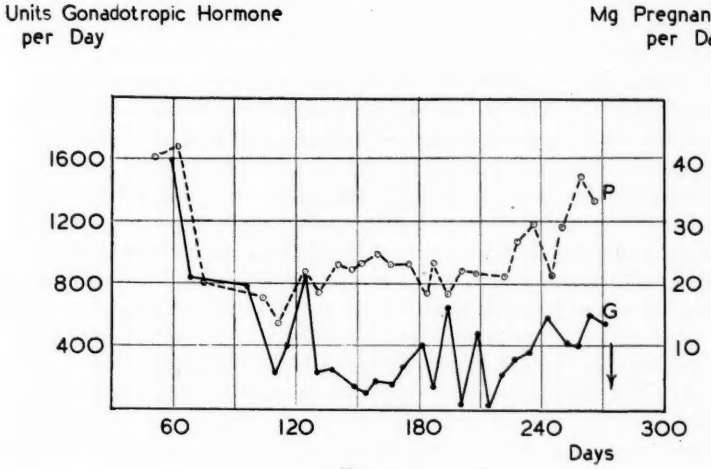

Fig. 1.

Excretion of gonadotropic hormone and pregnandiol in a normal pregnancy.

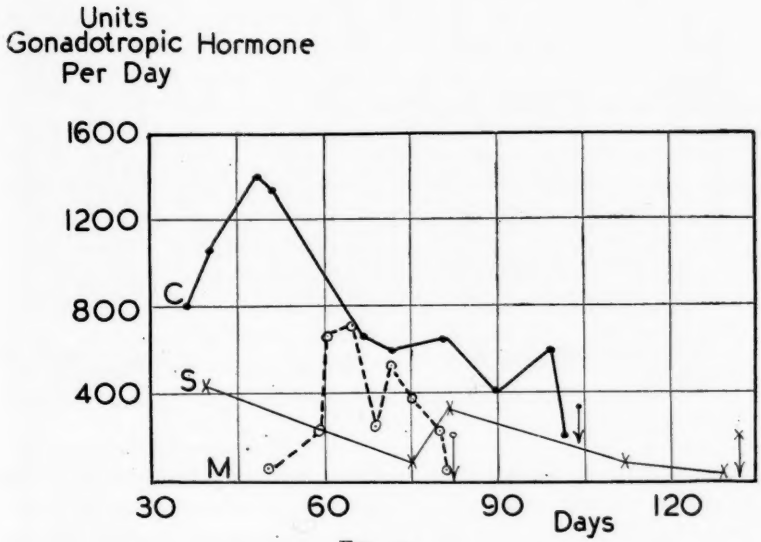

FIG. 2A.

Excretion of gonadotropic hormone in three cases which aborted while receiving progesterone treatment. Treatment was begun on forty-third day (S), fifty-eighth day (C), and sixty-fourth day (M).

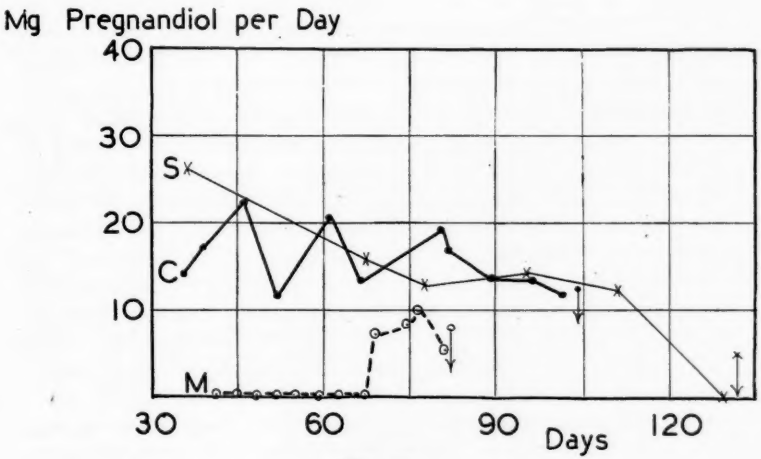

FIG. 2B.

Excretion of pregnandiol in the same three cases.

A study of the women who aborted shows that there was a low excretion of gonadotropic hormone at the time when the excretion should be high, and that the progesterone therapy was not appreciably affecting it. Figure 2A shows the excretion of the gonadotropic hormone in 3 women who aborted while under treatment. Two of them, *C* and *M*, show a peak in the excretion at about the expected time, but in both, and especially in *M*, the magnitude was much less than in the normal cases. In the third case shown, *S*, the peak may have been missed owing to the infrequency of the assays, a regrettable circumstance which was beyond our control. In a subsequent preg-

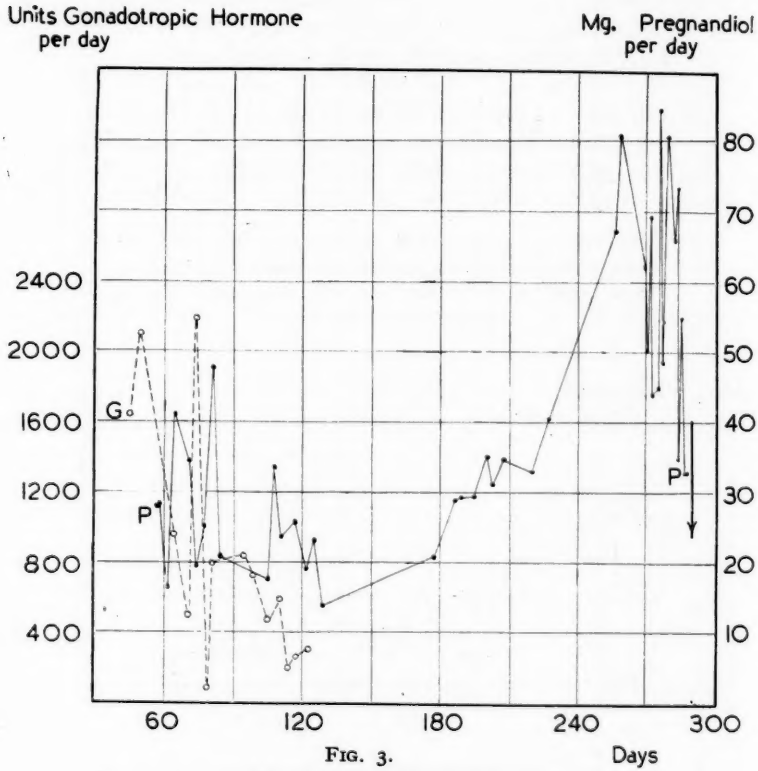

FIG. 3.

Excretion of gonadotropic hormone and pregnandiol in a successful case of progesterone therapy. This case had aborted on a previous occasion, which is shown in FIG. 2C. Therapy was begun on the forty-fourth day.

nancy, and with increased doses of progesterone, the pregnancy of one of these women, *C*, continued to term, and on this occasion the high excretion of gonadotropic hormone duly occurred between the sixtieth and seventieth days of the pregnancy. (Fig. 3.) On the other hand, successful results were obtained with progesterone therapy in one case (Fig 4) which did not show the normal early high excretion of hormone. In this case assays were made with sufficient frequency to exclude the possibility of the normal increase having escaped observation; all that could have occurred was a small and fleeting increase.

Whether or not the early high excretion occurred, the women in whom, under progesterone therapy, the pregnancy successfully continued to term, showed a steady, continued excretion of gonadotropic hormone, whereas those who aborted showed a steady fall, often to zero.

Excretion of Pregnandiol.

In a normal pregnancy our results (Fig. 1) show the pregnandiol excretion to be relatively high between the sixtieth and eightieth days of pregnancy, i.e. at the time when the excretion of gonadotropic hormone is also high. Thereafter, along with the gonadotropic hormone, it falls to a relatively low level at which it remains until about the two hundred and fortieth day, when it again rises rather sharply. This second high level is maintained until immediately before parturition. After parturition pregnandiol appears in the urine for a day or two, and then only in decreased amounts. These results agree only partly with those of Browne, Henry and Venning,[5] who found a daily excretion of 4 to 10 milligrams of pregnandiol up to the sixtieth day of pregnancy, and increase dating from the eightieth to the hundredth day, reaching 40 milligrams per day at the hundred and fiftieth day, and continuing to a peak in the eighth month, when two women showed an excretion of 80 and 70 milligrams respectively. These authors point out, however, that they cannot from their results determine the limits of normal variability. Our results differ from theirs chiefly in the high early excretion, an excretion which roughly parallels the high excretion of gonadotropic hormone at the same time, and which occurs too regularly in our series to be merely fortuitous.

As to the treated cases of recurrent abortion, the essential for success seems to be the maintenance, during the period from the sixtieth day to the two hundredth day of gestation, of a pregnandiol excretion about the normal level (Figs. 3 and 4; con-

trast Fig. 2B). There may or may not be a greatly increased excretion about the sixtieth day, depending, apparently, upon whether or not the gonadotropic hormone excretion is high at that time (Fig. 2B). There may even be some rise in the pregnandiol excretion during treatment followed by abortion, if the subsequent fall reaches too low a level. Irrespective of the height of the excretion-rate about the sixtieth day of pregnancy, in all successful cases the women show a maintained excretion during the middle months of about 20 milligrams per day of pregnandiol. The general tendency in all cases, successful or otherwise, was for the pregnandiol excretion to parallel the gonadotropic hormone excretion.

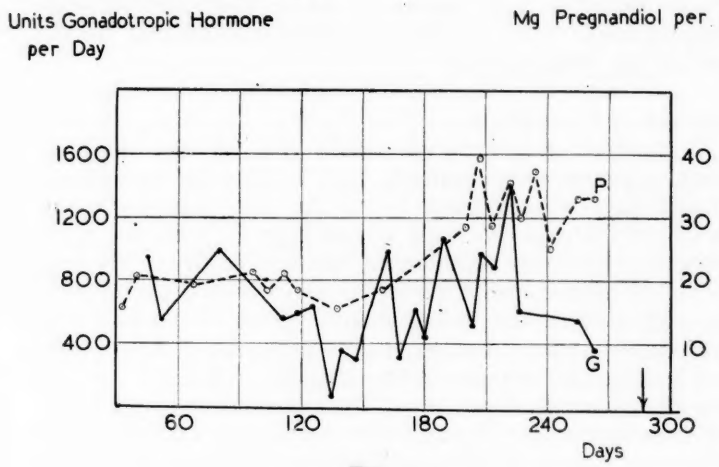

FIG. 4.

A successful case of progesterone therapy in which the normal high excretion of hormone at the third month of gestation did not occur. Therapy was begun on the fifty-first day.

Discussion.

The hypothesis to which these results have led us is briefly as follows. The high production of gonadotropic hormone at about the fiftieth to the sixtieth day of pregnancy, possibly of trophoblastic origin, causes intensive stimulation of the corpus luteum, possibly by the mediation of oestradiol, and, therefore, a high production of progesterone. This is responsible for effective placental growth. Given this stimulus, the placenta is able, by the eightieth or ninetieth day, to form a sufficient supply

of progesterone to maintain the pregnancy, and the corpus luteum can decrease in activity without danger of abortion. Though not essential to the hypothesis, there is evidence to suggest that the continued production of gonadotropic hormone also becomes a function of the placenta. The idea of production of progesterone by the placenta is supported by the work of, for example, Jones and Weil,[2] who found that it was possible to maintain pregnancy and to extract pregnandiol from the urine after the corpus luteum had been removed at the third month of pregnancy. We regard it as probable that the placental formation of progesterone is largely, though not necessarily entirely, independent of the gonadotropic hormone. Otherwise it becomes difficult to explain the increased pregnandiol excretion towards the end of pregnancy at a time when Venning and Browne[4] and others, as well as ourselves, have not observed any very marked corresponding increase in the excretion of gonadotropic hormone.

The sequence of events we visualize is: the pituitary gland through its secretion of gonadotropic hormone stimulates the ovary and so the production of progesterone; this in turn stimulates placental production of gonadotropic hormone which reacts on the ovary; the corpus luteum ultimately stimulates placental activity to the point at which it also begins to secrete progesterone; thereafter the corpus luteum diminishes in activity.

On this hypothesis the danger period in pregnancy is during the time when placental activity is developing and the corpus luteum activity is retrogressing. It is well known, in fact, that this danger period is towards the ninetieth day of pregnancy, just the time when the early high excretion of hormones is settling down to a steady, relatively low rate.

The hypothesis adequately explains:

(*a*) The fact that in hypophysectomized animals pregnancy can be maintained by administration of gonadotropic hormone [6] or oestradiol,[7] or progesterone.[8]

(*b*) The maintenance of pregnancy when the corpus luteum is removed at a time when the placenta is producing, or is on the verge of producing, progesterone.

(*c*) The common occurrence of abortion in the third month of pregnancy.

(*d*) The observed fluctuations in the excretion of gonadotropic hormone and pregnandiol.

Although we suggested the placenta as the probable site of progesterone and gonadotropic hormone formation during the

later months of pregnancy, it is possible that other glands, for instance the adrenals, may be concerned. That the placenta is at least the main site is, however, suggested by the rapid disappearance of pregnandiol and gonadotropic hormone from the urine after parturition.

The Clinical Results.

In Table II we have summarized the history with respect to previous abortions and the results of treatment in 20 patients. No case in which women had fewer than 2 successive abortions is included, and prior to progesterone treatment, 65 pregnancies had, altogether, resulted in only 10 live births. In none of these patients could any cause be found for the recurrent abortions—other, that is, than the hormone deficiency revealed in many of them during our investigation. Of the 22 pregnancies during which progesterone was given, there were, on the other

TABLE II.

Case No.	No. of previous abortions.	Mg. of progesterone administered.	Result.
1.	3	68	Success
2.	4	70	Success
3.	3	73	Success
4.	2 *a*	45	Failure
	3 *b*	410	Success
5.	2	15	Failure
6.	2	120	Success
7.	3 *a*	3	Failure
	4 *b*	33	Failure
8.	3	85	Success*
9.	2	66	Success
10.	3	80	Success
11.	3	23	Success†
12.	2	190	Success
13.	3	10	Failure
14.	4	50	Failure
15.	2	12	Failure
16.	2	55	Success
17.	2	43	Success
18.	3	74	Success
19.	2	49	Success
20.	4	8	Failure

* Z.A. weak, positive at beginning of pregnancy.

† Child lived only one day.

hand, only 8 which ended in abortion, whereas 14 resulted in a living child at term.

Superficially this appears a striking result in favour of progesterone therapy, but it is necessary to examine it a little critically. According to the calculations of Malpas the chance of a full-time pregnancy following a sequence of 2 abortions is 62 per cent, following 3 successive abortions 27 per cent, and following 4 successive abortions 6 per cent. If it be accepted that our suggestion as to the incidence of recurrent abortion agrees better with the data of Whitehouse, these figures are reduced to 47 per cent, 14.6 per cent, and 3 per cent respectively. The 22 women receiving progesterone treatment in our series had all a previous history of at least 2 abortions, and the percentage of live births was 64, a figure not significantly above the 62 of Malpas, though definitely above the 47 per cent which we have suggested. However, 13 of the women in our cases had 3 or more successive abortions prior to the treated pregnancy and, if this be taken into account, the expectation of a full-time pregnancy becomes only 40 per cent on Malpas's calculations, or 27 per cent on our own. Obviously the observed 64 per cent of successes in the women receiving progesterone is definitely greater than the percentage to be expected without treatment. The same conclusion is reached if one considers separately those women with a previous sequence of only 2 abortions and those with a sequence of 3 or more. In the former group (9) there were six successes and three failures, almost exactly the figures to be expected on the calculations of Malpas. In the second group (13), however, there were eight successes, whereas only three were to be expected without specific therapy.

The results we have obtained are in full agreement with those reported by other workers. Thus in a series of cases given by Bishop,[9] 8 with a history of 2 or more successive abortions the women were treated with progesterone to completion; of these 6 resulted in delivery at term, whereas the expected number was not more than 4. Kane[10] reported 40 pregnancies treated with progesterone, of which 36 went to term; from the previous history of these cases the expected number of pregnancies at term can be calculated as 26. In Elden's[11] series of 8 cases, 6 were successful. Malpas[2] also reports observations of his own and refers to others, concluding that "progesterone therapy probably represents the most effective method we possess of treating some cases of threatened abortion". He believes,

however, and we agree, that more chemical data are needed to determine the scope of the treatment.

Even as they stand, we are of the opinion that our figures definitely support the use of progesterone therapy in cases of recurrent abortion, and it should be noted that we have included in the series as "failures" cases in which treatment was only begun when abortion was actually threatening. We believe that when progesterone is given early enough, the proportion of successes can be still further increased. The majority of our failures occurred early in the investigation, when we were using very small doses of progesterone—for example, 1 milligram twice weekly—in conformity with current practice. More recently, in the light of our measurements of pregnandiol excretion, we have increased the dose, first to 3 milligrams and later to 5 milligrams, or even 10 milligrams and 20 milligrams twice weekly, with intensive therapy in cases of threatened abortion. Even these doses are surprisingly small to be effective, and there is almost an air of the miraculous about the results reported by various observers on doses which are almost infinitesimal in comparison with the amount of progesterone produced in normal pregnancy.

The mode of action of progesterone is obscure, but there is no doubt that its presence in adequate amounts is necessary for the maintenance of pregnancy. A study of the hormone excretion in cases of recurrent abortion at once indicates that in them there is a decreased output of the hormones during the early weeks of pregnancy as compared with normal cases. It has been shown,[12] too, that if progesterone is present in excessive amounts at term, parturition does not occur, and pregnancy is prolonged. The inference is that in cases of recurrent abortion, either the pituitary stimulus to the corpus luteum is weak, thus causing imperfect placental development, or the response of the corpus luteum to anterior pituitary stimulation is weak, thus giving the same result. The simplest explanation of the action of progesterone therapy in preventing abortion would be that it provides, by replacement, an adequate supply of an essential hormone until, whether by its stimulant action on the placenta or by an independent placental development, the deficiency is made good from natural sources. When one considers the smallness of the doses which appear to be effective in relation to the normal daily output of pregnandiol, it seems that this simple explanation of replacement therapy can only be correct if the margin between an adequate and an inadequate proges-

terone production is extraordinarily narrow. This, however, is not entirely impossible, though it seems unlikely in view of the case reported by Jones and Weil in which pregnandiol could not be detected in the urine for nearly a week after removal of the corpus luteum and yet the pregnancy continued to term. There is this consideration, of course, that during the critical period the patient in this case was, presumably, resting in bed after an abdominal operation.

It may well be, and indeed it is suggested by many facts, that while a temporary deficiency of progesterone does not in itself necessarily lead to abortion, it does make abortion an almost inevitable consequence of slight trauma or strain which would otherwise be without effect. If such is the case, the possibility arises that some accidental abortions may be potentiated by a temporary deficiency of progesterone due to some non-recurrent cause.

The administration of progesterone in relatively small amounts may be sufficient to maintain, or even stimulate, placental function over the critical period when the corpus luteum secretion decreases and the placenta is becoming a secretory organ. A study of the hormone excretion in normal pregnancy has suggested that this critical period is round the ninetieth day of gestation, and this is recognized as a common period for abortion to occur. In recurrent abortion, however, the critical period may be much earlier, as the hormone excretion may be at a sub-normal level at a very early stage.

Although an injection of a few milligrams of progesterone represents only part of a normal day's production as measured by the pregnandiol excretion, it gives, for a short time, an abnormally high concentration of the hormone in the blood. It is possible that this high concentration, repeated at intervals though not lasting long on each occasion, may provide sufficient extra stimulus to the developing placenta, and so enable it to take over its proper work of hormone production.

Neither of these explanations is entirely satisfactory, but on the evidence at present available we are unable to suggest one that is. The two are not mutually exclusive, and though we ourselves incline to the first as a working hypothesis, we recognize that both may contain some element of the truth but that, on the other hand, both may be wrong. Either, it may be noted incidentally, leads to the conclusion that progesterone therapy throughout pregnancy is usually unnecessary, and that most cases of recurrent abortion should be successfully treated by

administration of progesterone until the end of the fourth month of gestation. If further work should show this not to be the case, then both explanations fall to the ground.

ACKNOWLEDGMENTS.

We have to thank Messrs. Organon Ltd. for the progesterone used in this work, and the Medical Research Council for a grant which provided us with technical assistance and defrayed the cost of materials. Our thanks are also due to various colleagues who have placed cases at our disposal, and to Professor F. A. E. Crew for facilities in the Institute of Animal Genetics. We wish also to acknowledge the conscientious work of our technical assistants, Mr. Rae, Miss Wilson, and Miss Sanders.

REFERENCES.

1. Jones, W. H., and P. G. Weil. *Journ. Amer. Med. Assoc.*, 1938, cxi, 519.
2. Malpas, P. *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1938, xlv, 932.
3. Venning, E. M. *Journ. Biol. Chem.*, 1937, cxix, 437.
4. Browne, J. S. L., and E. M. Venning. *Lancet*, 1936, ccxxxi, 1507.
5. Browne, J. S. L., J. S. Henry, and E. M. Venning. *Journ. Clin. Invest.*, 1937, xvi, 678.
6. Robson, J. M. *Journ. Physiol.*, 1937, xc, 145.
7. Robson, J. M. *Journ. Physiol.*, 1939, xcv, 83.
8. Robson, J. M. *Journ. Physiol.*, 1936, lxxxvi, 415.
9. Bishop, P. M. F. *Guy's Hosp. Reports*, 1937, lxxxvii, 366.
10. Kane, H. *Amer. Journ. Obstet. and Gynecol.*, 1936, xxxii, 110.
11. Elden, C. A. *Amer. Journ. Obstet. and Gynecol.*, 1938, xxxv, 648.
12. Snyder, —. *Bull. Johns Hopkins Hosp.*, 1934, liv, 1.

Discussion on Dr. Macgregor's paper at the Eleventh British Congress of Obstetrics and Gynaecology (April 1939).

Dr. BETHEL SOLOMONS asked the following questions:—

(1) Was the ovum examined for degeneration in any of the cases in which abortion had occurred?

(2) Were other treatments, such as wheat germ oil, or rest, used?

(3) Was the male examined for faulty spermatogenesis?

He had had several cases of habitual abortion due to the last cause. He said that the cost of a treatment as outlined by Dr. MacGregor would be nearly prohibitive, and suggested that this disadvantage could be removed if the firms making hormonic preparations could induce veterinary surgeons to make more use of them in their work. The greater the amount prescribed, the cheaper would be the cost.

This was the kind of paper which was an example to writers for future congresses.

The Complications of Radium Therapy in Cancer of the Uterine Cervix*

BY

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ALTHOUGH the treatment of cancer of the uterine cervix is now almost entirely radiological, the best method of irradiation is still unsettled. The merit of any technique is customarily assessed on its five-year salvage, but this is unsatisfactory in so far as judgment is based on an incomplete picture of the results of therapy. The wide employment of radium in advanced cancers demands an evaluation of its effects from the standpoint of palliation as well as of cure, and this is not possible without some knowledge of the dangers associated with its use. It is the purpose of this investigation to examine the complications of therapy in 650 consecutive cases of cervical cancer irradiated in the Gynaecological Department of the Cardiff Royal Infirmary. In the earlier years the supply of radium was contained in 12 needles with a screenage of 0.5 mm. of platinum, which were embedded in and about the tumour as previously described by Strachan.[1] From 80 to 120 mg. of radium element were so applied, usually for a period of 24 hours. In 1930 interstitial irradiation was abandoned in favour of a fractional intracavitary method based on the technique introduced by Heyman of Stockholm, and this is the method still employed. A tube of 50 mg. of radium is placed in the uterine cavity, when this is easily effected, and one or more silver boxes containing a total of 50 to 80 mg. are apposed to the vaginal aspect of the growth. The applicators are enveloped in thin rubber and screenage is the equivalent of 1.5 mm. of platinum. Two exposures, each usually of 30 hours, are given, separated by an interval of one week. In both methods the vagina is firmly packed with gauze, and an indwelling catheter is used during irradiation. The patient subsequently receives a daily vaginal

* From the Department of Obstetrics and Gynaecology Welsh National School of Medicine.

douche, and is instructed to continue douching for some weeks after leaving hospital. It may be noted that in addition to the surface method of application and the slightly longer fractional exposure, the main features introduced with the cavitary technique were increased filtration and the employment of a uterine radium container.

Cancer patients after irradiation are exposed to complications directly attributable to treatment, and to others caused by the continued extension of the disease. This review is concerned with all such developments, so may include conditions for which therapy is not entirely responsible. Its objects are twofold, namely to examine the incidence of the major complications of irradiated cervical cancer, and to compare the relative risks of two forms of irradiation. The sequelae observed were immediate and remote. Of the earlier complications, the more common were either irritative or inflammatory.

Proctitis and Cystitis. Both bladder and rectum are exposed to the irritative effects of the rays, but with modern methods the risk of serious injury is small and may be minimized by fully distending the anterior and posterior vaginal fornices with gauze. Firm vaginal packing maintains the radium in position and displaces the bladder and rectum from the centre of its field of influence, and further protection is afforded to the bladder by the routine use of a self retaining catheter. Of the two viscera, the rectum is by far the more sensitive, and in comparison the bladder seems to be relatively resistant to the rays. In our experience, symptoms of vesical irritation were inconspicuous, and although proctitis occurred in a small proportion of the cases, it was rarely troublesome.

Inflammatory complications. The most alarming complication of radiotherapy in cervical cancer is spreading bacterial infection. The carcinomatous cervix harbours various strains of streptococci as well as less virulent organisms, and infection may involve deeper structures. This may take the form of pyometra, which was a pre-radiation complication in 12 cases of this series (1.85 per cent). The women so affected were over 54 years of age which is some indication of its close association with post-menopausal uterine atrophy. The condition responded promptly to drainage, and when the case was subsequently irradiated no serious inflammatory complication supervened, although in one case the pyometra recurred.

Pyometra. Until recent years, malignant disease of the uterus was the only common cause of pyometra, but the latter

is nowadays a well-recognized sequel of local irradiation of the female genital tract. Instrumentation is liable to convey organisms to the endometrium and spread of infection is still further encouraged by vaginal packing. Pyometra may follow radiotherapy for metropathia (Brooke Bland[2]), and in cervical cancer the risk of this complication is considerably greater. Retention usually occurs in an organ that has undergone senile atrophy in conjunction with varying degrees of cervical occlusion. This may arise within a few days of irradiation as a result of oedema, or years later as a fibrotic stricture in the process of healing. Post-radiation pyometra occurred in 8 cases (1.23 per cent), all in women with advanced disease, and only one was less than 50 years of age. In 4 cases the condition developed immediately after the first exposure and necessitated the temporary postponement of the completion of treatment, and in 3 others it developed within 12 months of irradiation.

In the remaining case the pyometra was a late development with the following history:

> A woman, 60 years of age, with a stage 3 carcinoma was treated by the interstitial method in 1929. Her health improved until 1934 when she commenced to complain of occasional headache and lower abdominal discomfort. There was no sign of recurrence, but her symptoms continued, and she steadily lost weight until 1936 when admission to hospital was recommended and a pyometra was drained *per vaginam*. She has since enjoyed good health.

It will be observed later that serious inflammatory sequelae were more common with the cavitary method of treatment, and this is also true of pyometra. For purposes of comparison an analysis is made of 500 women irradiated 3 or more years ago. Of this number 7 developed pyometra (1.4 per cent). The complication was observed twice among 248 cases after needling (0.8 per cent), and on 5 occasions in 252 cases treated by the cavitary technique (1.98 per cent). Drainage was effected by dilatation of the cervix, but cases are recorded with complete atresia of the cervix, when hysterectomy may be required (Healy[3]).

Fatal infection. Twelve women died of inflammatory complications within a month of irradiation (1.85 per cent). They were all subjects of advanced carcinoma. In 2 cases death was precipitated by acute pyelonephritis which supervened on grossly damaged kidneys; 2 patients died of septicaemia, and the remaining 8 of peritonitis. Fatal inflammatory sequelae were more

common with the cavitary technique. Four hundred and two patients were treated by this method with 10 fatalities (2.48 per cent), while 2 fatal cases occurred in 248 women after interstitial irradiation (0.8 per cent). It would be rational to expect the needling of an infected ulcer to predispose to the spread of organisms, but these findings suggest that factors of greater importance are operative in the cavitary method of treatment, and one of these seems to be the employment of a uterine radium container. For this reason some authorities rely entirely on vaginal applicators for local irradiation (Burnam[4]), and this has been our practice when the external os is not readily located. In many advanced cancers location of the cervical canal is not possible, and the uterine tube was omitted either from choice or necessity in approximately 25 per cent of our material. It is noteworthy that the incidence of fatal infection in this group was only one third as great as in the cases which received complete treatment.

Fatal Inflammatory Complications of Cavitary Technique.

	Uterine tube employed.		*Uterine tube omitted.*		*All Cases*	
Stage.	Cases treated.	Deaths.	Cases treated.	Deaths.	treated.	Deaths
1	30	—	—	—	30	—
2	70	—	10	—	80	—
3	176	7 (3.9%)	53	—	229	7 (3%)
4	23	2 (8.6%)	40	1 (2.5%)	63	3 (4.7%)
	299	9 (3%)	103	1 (0.9%)	402	10 (2.48%)

Primary mortality. Although the most serious of the early complications of irradiation are usually inflammatory in character, other incidents contribute towards its immediate risks. According to published reports the primary mortality of radium treatment in cancer of the cervix ranges from 1 per cent to 4 per cent. Brooke Bland states that in 2,548 cases collected from the literature the figure was 2.5 per cent, but that in France, probably on account of the longer exposure employed, it was in excess of 4 per cent (Findley[5]).

In this series 17 women succumbed within a month of treatment, a primary mortality of 2.6 per cent. Of this number 14 died after the first course of therapy, and in 3 cases death followed

re-radiation several years after initial treatment. As previously noted, 12 fatalities were due to inflammatory sequelae, and of the 5 remaining patients, one died of embolism, and the other 4 became weaker and died without adequate cause being found either clinically or at autopsy. The pathology of this collapse which is liable to follow irradiation is not clear, but Jeanneney and Authié[6] suggest that it is related to the intoxication which follows the disintegration and absorption of the tissue proteins of the neoplasm.

The mortality of treatment was nil in the case of moderately early lesions, but it increased steadily with the degree of advancement of the carcinoma, and of the two forms of treatment, the cavitary method, in virtue of its tendency to infective sequelae, was associated with the greater immediate risk.

Primary Mortality of Radium Treatment.

	Cavitary Method.		*Interstitial Method.*		*All Cases.*	
Stage.	Cases treated.	Deaths.	Cases treated.	Deaths.	treated.	Deaths.
1	30	—	15	—	45	—
2	80	—	43	—	123	—
3	229	10 (4.4%)	180	3 (1.6%)	409	13 (3.1%)
4	63	4 (6.3%)	10	—	73	4 (5.5%)
	402	14 (3.4%)	248	3 (1.2%)	650	17 (2.6%)

Intestinal obstruction. Intestinal obstruction is a late occurrence in cervical cancer, being usually due to malignant invasion of the rectum and sigmoid colon. Behney[7] found the lower bowel involved in 4.2 per cent of his autopsy material. The incidence of obstructive symptoms in this series is estimated in a group of 500 women irradiated more than 3 years ago. The complication was observed in 8 of these women (1.6 per cent), in 3 of whom it was a terminal event. The lesion was a carcinomatous stricture in the region of the junction of the rectum and sigmoid colon, with the exception of one patient in whom the small bowel was the site of metastasis. Four of the patients required colostomy, but only one survived the operation by more than two months.

Intestinal obstruction may rarely develop after radiotherapy as a result of benign stenosis of the bowel. Collins and Jones[8] have described 6 cases following combined radium and Röntgen irradiation of cervical cancer, 5 with non-malignant stricture of

the sigmoid colon, and one with the small bowel similarly affected. As the condition is curable by operation the authors stress the importance of submitting to laparotomy all patients exhibiting symptoms of intestinal obstruction following radiotherapy without evidence of gross carcinomatous recurrence.

Irradiation, in addition to possessing selective action on malignant cells, stimulates connective tissue proliferation, with stricture formation as a well recognized sequel. Extensive vaginal and rectal contractures were common in the early days of radiotherapy, and ureteric and urethral strictures have been described. Everett[9] has drawn particular attention to the frequency of ureteric strictures after pelvic irradiation, and records 3 cases following the radiological treatment of a myomatous uterus.

Fistula formation. Many contributions have been made to the literature on the incidence of fistulae in irradiated cervical cancer, but there is wide variation in the figures of various authors. As Graves *et alia*[10] point out, many of the published figures are too low, and being based on recently treated cases, give a totally erroneous view of the frequency of this complication. In 1931 Strachan[11] found fistulae in 8.7 per cent of 254 cases of cervical cancer treated with radium at Cardiff. Some of these patients had been recently irradiated and it was recognized that in many of the living group the disease was still active and the percentage of fistulae would inevitably increase. Three hundred and fifty cases have now been followed for a minimum period of 5 years or to previous death; and in this group there were 20 rectal, 13 vesical and 6 recto-vesico-vaginal fistulae, a fistula-incidence of 11 per cent. The fistulae all occurred in the presence of active disease at an average interval of 10 months after the first, and 7 months after the last irradiation, and 80 per cent appeared within 3 years of initial treatment, which is significant when the value of a 3-year follow-up is considered.

Fistulous communications usually result from the disintegration of carcinomatous tissue in the vaginal septa, and this natural sequence in the course of the disease may be accelerated by injudicious irradiation. A rare variety of fistula develops several years after radiotherapy in the absence of malignant disease, and is caused by obliterative endarteritis and ischaemic necrosis of the bladder base. This type of fistula was not observed in this series, but Graves *et alia* describe 6 cases occurring at an average interval of 4 years after irradiation.

The appearance of a fistula influences prognosis for the worse, and 60 per cent of the patients died within 6 months of

its occurrence. The average length of life subsequently was 10 months, but 2 patients lived for more than 2 years with vesical fistulae, and one woman is still alive 7 years after the development of a rectal fistula. Rectal fistulae following radiotherapy have been known to heal spontaneously (Findley), and Gray Ward[12] succeeded in closing two post-radiation bladder fistulae by operation.

It is now proposed to examine the bearing on fistula formation of certain variants, namely the local extent of the carcinoma, the microscopic and macroscopic characters of the growth, the dosage and mode of treatment, and for this purpose an analysis is made of a group of 500 women followed for a minimal period of 3 years.

Extent of the Carcinoma. The cases were grouped according to the classification recommended by the Radiological Sub-Commission of the League of Nations's Report, 1929. With moderately early lesions the risk of fistula was small, and the complication was not observed in a carcinoma of stage 1 or stage 2 after a single course of therapy. The following table shows the incidence of fistulae in the four clinical groups, with the interval between initial radiotherapy and the development of the fistula.

		Fistula developed during					Average interval between
Stage.	Cases treated.	First 6 months.	Second 6 months.	Second year.	Third year.	First 3 years.	initial radium and fistula.
1	32	—	—	—	1	1 (3.1%)	35 months
2	92	—	1	3	—	4 (4.3%)	17 ,,
3	325	9	9	7	1	26 (8%)	11 ,,
4	51	4	3	—	—	7 (13.7%)	4 ,,
	500	13	13	10	2	38 (7.6%)	

Macroscopic type of growth. The cancers were grouped into 3 naked-eye types. The ulcerative type which is commonest and ultimately leads to the destruction of the cervix, the proliferative type in which the growth is chiefly outward from the cervix, and the inverting type which is predominantly endocervical. Fistulae were more common in the ulcerative, and less common in the hyperplastic cancers, a distribution which would be expected in

view of the more invasive and destructive character of the former type.

Macroscopic type of cancer	Cases treated.	Fistulae.	Per cent.
Ulcer	307	30	9.8
Fungating	119	4	3.3
Endocervical	74	4	5.4
	500	38	7.6

Histological grade of carcinoma. The cancers were classified according to the predominant cell type (Maliphant[13]), and on this basis fell into 4 fairly distinct groups, 71 cases being excluded from this analysis since the biopsy material was either insufficient for reliable microscopic grading, or unsuitable on account of superadded inflammatory change. In the following table a comparison is made of the incidence of fistulae in the 4 histological groups, and it is observed that the complication was much more common in the spindle-cell cancers.

Histological grade of cancer.	Cases treated.	Fistulae.	Per cent.
Spinal	97	8	8.25
Transitional	256	16	6.2
Spindle	57	9	15.8
Adenocarcinoma ...	19	1	5.3
	429	34	7.9

Method of treatment. Interstitial radium was used in 248 cases, and 252 patients were treated by the cavitary technique. There was not any significant difference in the distribution of macroscopic and microscopic types of growth in the 2 groups, but fistulae were more than three times as common after needling. The dosage used in this method of treatment was relatively low, averaging 1,800 m.e.h., and its liability to fistula formation was presumably due to inadequate filtration.

Stages.	*Interstitial Method* Cases treated.	Fistulae.	Per cent.	*Cavitary Method.* Cases treated.	Fistulae.	Per cent.
1 and 2	58	4	6.0	66	1	1.5
3 and 4	190	25	13.2	186	8	4.3
	248	29	11.7	252	9	3.5

Dosage. The importance of screenage is now well recognized, so the influence of dosage on fistula formation is examined in women treated by the cavitary method and is restricted to cases in which the complication developed after a single course of therapy. For this reason 2 patients in whom fistulae appeared after re-radiation are excluded from this analysis. The figures in the following table indicate the danger of heavy dosage, particularly in the presence of advanced disease.

Stages.	Vaginal dosage not exceeding 4500 m.e.h. Cases treated.	Fistulae.	Per cent.	Vaginal dosage exceeding 4500 m.e.h. Cases treated.	Fistulae.	Per cent.
1 and 2	50	—		13	—	..
3 and 4	134	2	1.5	55	5	9.0
	184	2	1.08	68	5	7.35

Re-radiation. Fistulae were particularly common in cases which required re-radiation; 23 of the 38 patients with fistulae receiving more than one course of therapy; 40 per cent of this number were re-radiated on more than 2 occasions, while the corresponding figure for the entire series is 7 per cent. The need for further treatment implies continued extension of the malignant disease, and the contractures which develop about irradiated tissues increase the difficulties of therapy. Areas which have undergone fibrosis do not tolerate ordinary dosage, and it is necessary to limit the intensity of irradiation in order to reduce the risk of fistula formation.

Previous hysterectomy. One patient had previously been submitted to supravaginal hysterectomy and she developed a recto-

vaginal fistula. It is universally recognized that the irradiation of stump cancers must be undertaken with care, and Gray Ward has stressed the importance of reducing the usual dosage. Following hysterectomy the altered relation of the bladder increases its risk of injury, and this also applies to loops of bowel which may be adherent to the pelvic floor. It is in these cases that the comparatively rare ileo-vaginal fistulae have been described, when the patient's misery is aggravated by the irritating liquid nature of the faecal discharge.

Discussion.

The complications of radiotherapy in cervical cancer range from conditions associated with mild transient discomfort to those responsible for prolonged misery and disablement. With moderately early lesions, serious after-effects are exceptional, but when the disease is extensive treatment is more hazardous. Advanced cancers are usually heavily infected with vaginal septa thinned by malignant invasion, and radium treatment under these conditions is accompanied by two major risks: spreading bacterial infection and fistula formation. Post-radiation fistulae are becoming less common, now that the dangers of overdosage and low screenage are more fully appreciated. In our material the incidence of this distressing complication has fallen by 70 per cent since the adoption of the cavitary technique, a result which is probably entirely attributable to better filtration, and with a vaginal dose limited to 4,500 m.e.h. the fistula incidence at the end of 3 years is only 1 per cent. However, women irradiated by the cavitary method have shown an increased tendency to inflammatory sequelae with a corresponding rise in the primary mortality of treatment, and evidence is presented from which it seems justifiable to conclude that this is at least partly due to the employment of a uterine radium container. If the latter ensures a better ultimate result the increased risk of infection may well be incurred, but in cases of widespread disease when there is little prospect of cure and the cervical canal is not easily located, the uterine tube is often better omitted. Of the points which emerge from this survey one of the most important is the need for extra caution in the management of advanced cancers. It is in these cases that radiotherapy is associated with its greatest dangers, and indiscriminate treatment is followed by disastrous consequences which bring radium to disrepute and add to the sum-total of suffering. The number of patients reporting with advanced lesions unfortunately continues to be high, and while radium has much to offer

these women the scope and limitations of therapy first require review, and the aims of palliation are usually best achieved by the technique which enjoys the greatest freedom from untoward effects.

Summary.

The complications observed in 650 cases of irradiated cervical cancer are examined with the relative risks of two forms of treatment.

Therapy was associated with a primary mortality of 2.6 per cent, and the commonest cause of early death was peritonitis.

Inflammatory sequelae were more common with the cavitary technique, for which it is suggested that the employment of a uterine tube is at least partly responsible.

Post-radiation pyometra occurred in 1.25 per cent, and was usually seen in older women. 1.6 per cent developed intestinal obstruction, due in all cases to malignant involvement of the bowel.

The incidence of fistulae within 5 years of irradiation was 11 per cent. Fistula formation was usually a manifestation of advanced disease, and factors which predisposed to its occurrence were an ulcerative lesion, anaplastic histological pattern, interstitial radium, heavy dosage and repeated treatment. The adoption of the cavitary technique has resulted in a substantial fall in the incidence of this complication.

The risks of radiotherapy are small in moderately early cases, but when the cancer is extensive they require careful consideration.

References.

1. Strachan, G. I. "Technique of radium application in uterine carcinoma." *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1929, xxxvi, 367.
2. Bland, P. Brooke. "Pyometra following radium therapy of uterine cancer." *Amer. Journ. Obstet. and Gynecol.*, 1929, xvii, 528.
3. Healy, W. P. "Experience with radiation therapy in cancer of the cervix." *Amer. Journ. Obstet. and Gynecol.*, 1934, xxviii, 386.
4. Burnam, C. F. "Obstetrics and Gynaecology," iii, 868. (Edited by A. H. Curtis. W. B. Saunders & Co., Philadelphia and London, 1933.)
5. Findley, P. "Complications resulting from pelvic irradiation for cancer of the cervix." *Amer. Journ. Obstet. and Gynecol.*, 1934, xxvii, 358.
6. Jeanneney, G., and Authiè. "Fatal accidents in the radium therapy of uterine cancer." *Rev. franc. de gynéc. et d'obst.*, 1935, xxx, 677.
7. Behney, C. A. "Advanced carcinoma of the cervix, with a report of 166 necropsies." *Amer. Journ. Obstet. and Gynecol.*, 1933, xxvi, 608.

8. Collins, E. N., and T. E. Jones. "Benign stricture of the intestine due to irradiation of cervical cancer." *Surg., Gynec. and Obstet.*, 1934, lix, 644.
9. Everett, H. S. "Urological complications following pelvic irradiation." *Amer. Journ. Obstet. and Gynecol.*, 1934, xxviii, 1.
10. Graves, R. C., C. J. E. Kickham, and I. T. Nathanson. "Bladder complications of cancer of the cervix." *Surg., Gynec. and Obstet.*, 1936, lxiii, 785.
11. Strachan, G. I. "Radiotherapy and fistula formation in cervical carcinoma." *Journ. Obstet. and Gynaecol. Brit. Emp.*, 1931, xxxviii, 1.
12. Ward, G. G. "Complications of radium therapy in gynecology." *Amer. Journ. Obstet. and Gynecol.*, 1933, xxv, 1.
13. Maliphant, R. G. "Histological classification of cancers of the uterine cervix and the relation between cellular structure and prognosis after radium treatment." *Journ. Obstet. and Gynaecol. Brit. Emp,.* 1933, xl, 444.

Some Factors bearing upon the Haemoglobin Level in Pregnancy

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THIS paper contains the results of the determination of the haemoglobin in the blood of over 200 European and coloured women attending the antenatal clinic at the Peninsula Maternity Hospital, Cape Town, during a consecutive period of 15 months, and of an investigation into the effect on the haemoglobin level of age, number of pregnancies, and earnings.

Methods. Capillary blood from the finger was examined. It was obtained in the morning, 1 to 3 hours after breakfast, by a clean puncture with a mechanical stylette so that the blood flowed freely and squeezing the finger was avoided. One-tenth of a cubic centimetre was taken into a blood-sugar pipette and washed out into 5 cubic centimetres of $N/10$ hydrochloric acid. After 2 hours the haemoglobin was determined by reading the colour in a Hellige colorimeter, the mean of five or more readings being taken. The wedge of the colorimeter was re-calibrated against normal blood, the oxygen capacity of which had been determined by the method of Van Slyke and Neill.[1] Hufner's[2] factor was used to convert the oxygen capacity to grams of haemoglobin per 100 c.c. of blood. The observations were checked by a second person using a Zeiss step-photometer with filter S.43, and if the observations did not agree the determination was discarded. Hufner's factor was also used to convert the haemoglobin values in the literature to grams per cent.

The results were examined by the statistical methods recommended by Bradford Hill,[3] and the differences between means and percentages were considered significant when greater than twice the standard error of that difference. The method described by Tippett[4] for the examination of small samples was also used: the value of t was calculated, and the value of p was taken

from Fisher's[5] table. The means were taken to be different when p was less than 0.05.

Material. Patients were taken without selection from among those attending, but such as were found to have gross organic disease or evidence of tuberculosis or syphilis were rejected. An inquiry was made into the economic position of each; the information required was the total income of the household and the number of persons dependent on the income, adults and children alike counting as one unit. In a certain number this information could not be fairly assessed, and such persons were not considered in connexion with social status; in most of these cases the individuals were better off than would have appeared by the above criterion.

Five hundred and twelve observations were made on 235 women, consisting of 108 Europeans, 105 Cape coloured and 22 Natives (Kaffirs).

Results.

The grand mean of all observations on 213 Europeans and Cape coloured was 12.40 grams of haemoglobin per 100 c.c. of blood. The standard deviation was 1.053 and the standard error of the mean 0.072.

Table I.

	Duration of pregnancy	Number of patients	Mean haemoglobin	σ	Difference of means	Difference of means / Standard error of difference
	Weeks		Gm. / 100 c.c.			
Europeans	26 to 32	36	11.74	1.77		
	33 to 36		11.80	1.73	0.06	0.15
	33 to 36	43	12.18	1.04		
	37 to 40		12.35	1.40	0.17	0.64
Coloured	26 to 32	16	12.26	1.27		
	33 to 36		12.13	1.05	0.13	0.32
	33 to 36	26	11.88	0.88		
	37 to 40		12.06	0.92	0.18	0.75
All Europeans		108	12.48	1.029		
All coloured		105	12.32	1.125	0.16	1.08
All coloured		105	12.32	1.125		
Natives		22	11.64	1.57	0.68	1.94

1. *Effect of Duration of Pregnancy.*

Thirty-six Europeans had been seen before the 32nd week of pregnancy and again between the 33rd and 36th weeks; the mean of the earlier observations was compared with the mean of the later. The details are given in the first two lines of Table I: the difference of the means (column 6) is 0.06, and this divided by its standard error gives 0.15 (column 7); for the difference to be statistically significant the last value should be 2 or more. In the same way the mean of 43 Europeans seen between the 33rd and 36th weeks was compared with the mean of the same persons seen after the 36th week (lines 3 and 4 of the table). The coloured were treated in the same way. The table shows that there was no change in the mean haemoglobin level in these three periods in the third 3 months of pregnancy.

Since the duration of pregnancy did not appear to affect the haemoglobin at this stage of pregnancy, and since all the patients had reached this stage, this factor was neglected in the subsequent analyses, and in those cases in which more than one determination was made the average value was taken; in more than half of the patients this was possible.

2. *Europeans, Coloured and Natives.*

Table I shows that the difference between the mean haemoglobin of the Europeans and of the coloured was barely greater than the standard error of that difference. It is, therefore, unlikely that there is a difference in the haemoglobin levels of the two peoples. The standard deviations were of the same size.

The haemoglobin of the Natives was lower than that of the coloured by 0.68 grams. The value of p was 0.02, so it is improbable that this difference was due to chance.

3. *Number of Pregnancies and Age.*

Table II shows the variation of the mean haemoglobin level with the number of pregnancies, the European and coloured women being taken together. The primigravidae had the highest level, and calculation of t showed that their mean haemoglobin was significantly greater than that of the multiparae; p was less than 0.01. It appears from the table that after the first baby the haemoglobin level is 0.5 gram lower than before, but that the effect of subsequent pregnancies is irregular and not to increase this deficit.

The effect of parity might also be shown in a greater incidence

TABLE II.

Effect on Haemoglobin of Number of Pregnancies.

Pregnancy	Number of patients	Mean haemoglobin	σ
		Gm. / 100 c.c.	
First	83	12.71	0.937
Second	57	12.29	0.98
Third	27	12.29	1.14
Fourth	18	12.17	0.63
Fifth	7	12.46	1.16
Sixth and over	19	12.07	1.18
Multiparae	128	12.24	1.033

of individuals with low haemoglobin level. A haemoglobin level of under 11 grams occurred three times among 83 primigravidae (3.6 per cent) and 11 times among 128 multiparae (8.6 per cent). The difference, 5 per cent, has a standard error of 3.3, so it may very well be due to chance.

The age of 25 divided the women into approximately equal groups. The mean haemoglobin level of the younger group was 0.29 gram greater than that of the older (Table III). The difference

TABLE III.

Effect of Age and Parity on Haemoglobin.

Age	Parity	Number of patients	Mean haemoglobin	σ	Difference of means	*p*
			Gm. / 100 c.c.			
Over 25		100	12.36	0.940		
Under 25		94	12.65	1.071	0.29	0.05
20 to 22.5	Primigravidae	18	12.44	1.27		
	Multiparae	14	12.62	0.72	0.18	0.6
22.5 to 25	Primigravidae	21	12.85	0.54		
	Multiparae	25	12.05	1.34	0.80	less than 0.02
25 to 27.5	Primigravidae	13	12.77	0.92		
	Multiparae	19	12.14	0.66	0.63	less than 0.05
27.5 to 30	Primigravidae	6	12.86	0.97		
	Multiparae	17	12.12	0.77	0.74	between 0.1 and 0.05

is small but seems to be significant, since p is 0.05, but it is probably due to the presence of 58 per cent of primigravidae in the younger group and only 22 per cent in the older.

Of the primigravidae 87 per cent were aged between 17.5 and 30 years, the remainder being widely scattered. The means for successive $2\frac{1}{2}$-year periods from $17\frac{1}{2}$ years on were 12.5, 12.4, 12.8, 12.8, and 12.9. There was, if anything, an increase of haemoglobin with age.

Table III contains the result of comparing primigravidae with multiparae in $2\frac{1}{2}$-year groups. At age 20 there was no difference; at 22.5 and 25 the primigravidae had significantly more haemoglobin, and at 27.5 they still had more, but the excess was of doubtful significance, p being between 0.05 and 0.1. The influence of parity is, therefore, clear.

Haemoglobin levels under 11 grams occurred three times among 57 primigravidae under 25 years (5.3 per cent) and not once among 25 over that age; the difference is 5.3 per cent, and its standard error 2.97. They occurred five times among 40 multiparae under 25 (12.5 per cent) and four times among 83 over 25 (4.8 per cent); the difference is 7.7 per cent, with a standard error of 5.7. In both instances the difference may be a chance one, but in each instance the older women have the advantage.

There seems little doubt that during the first half of the childbearing period age has no effect on the haemoglobin level, unless it be a favourable one.

4. *Economic Status.*

The different ways of life of the coloured and the Europeans make it necessary to consider them separately.

Coloured. The mean weekly income, without deduction for rent, was 10*s.* $1\frac{3}{4}$*d.* per head, with a standard deviation of 4.99 shillings. The coloured women were divided into groups with incomes above and below 10*s.*; the mean haemoglobin level of the former was 12.36 and of the latter 12.19, but as p is 0.4, the difference may very easily be due to chance. A haemoglobin level below 11 grams occurred six times among 63 women in the poorer group (9.5 per cent), and once among the 28 better-off (3.6 per cent); the difference, 5.9 per cent, has a standard error of 5.1 and may very likely be due to chance.

European. The mean weekly income of those from whom satisfactory data could be obtained was 21*s.* 6*d.*, with a standard deviation of 11.4 shillings. The mean haemoglobin of those living

TABLE IV.

Effect on Haemoglobin of the Economic Status.

Race and income	Number of patients	Mean haemoglobin	σ	Difference of means	Difference of means / Standard error of difference	p
		Gm./100 c.c.				
Coloured under 10s.	63	12.19	1.029			
Coloured 10s. and over	28	12.36	0.777	0.17	0.87	0.4
European under £1	46	12.10	1.014			
European £1 and over	52	12.67	0.919	0.57	2.9	0.01−.
European £1 and over	52	12.67	0.919			
All coloured and European under £1	137	12.19	0.990	0.48	3.12	0.01−.
European under £1	46	12.10	1.014			
All coloured	91	12.24	0.97	0.14	0.77	0.4+.

on more than £1 per head was 12.67 and of those living on less 12.10; this difference is significant. The means at different rates of earning showed little increase after the 15*s.* level was exceeded.

Haemoglobin levels under 11 occurred 6 times among 52 of the poorer (11.5 per cent) and once among 46 with more than £1 (2.2 per cent). The difference, 9.3 per cent, has an error of 4.9.

European and coloured. Among the coloured women there were only four receiving £1 per head and only one receiving more. When all the coloured and Europeans with less than £1 were compared with the remaining Europeans, it was found that the mean of the first group was nearly 0.5 gram less than that of the second; p was less than 0.01 so the difference is certainly significant.

Haemoglobin levels under 11 occurred in 9.1 per cent of the first and in 2.2 per cent of the second; the difference, 6.9 per cent, has an error of 3.2 and so is probably a real one. The mean haemoglobin of the poorer Europeans was not significantly different from that of all the coloured, and haemoglobin levels under 11 occurred in 11.5 per cent of the former and in 7.7 per cent of the latter; the difference, 3.8 per cent, has an error of 5.2, so it may easily have been due to chance.

Discussion.

There are surprising differences in the levels of haemoglobin which are accepted as normal for women by different authorities. Haldane[6] in 1901 gave 12.4 grams per 100 c.c. as the normal, but recent figures are definitely higher, especially those from America and Germany. Price-Jones[7] found a mean of 13.6 grams in London women, and this figure has been accepted by most recent English authors. Dor and Lambrechts[8] found a mean of 13.78 in Belgium, and Heilmeyer[9] gives 14 to 18 as the range of normal in Germany. Peters and Van Slyke[10] combined reliable American data and concluded that for women from 16 to 60 years of age the mean oxygen capacity was 19.0 volumes per cent, which, converted by Hufner's factor, corresponds to 14.1 grams of haemoglobin. Sokhey[11] found a mean of 12.9 in India, but Rao[12] who, however, studied a population living at a high altitude, obtained one of 15.8. Part of these discrepancies may be due to the use of different methods and of unchecked clinical haemoglobinometers, which are liable to gross error (Wintrobe[13]), but Heilmeyer suggests that the standard of health has improved and that the mean haemoglobin has actually risen during the past 35 years. Price-Jones, however, showed that the haemoglobin level in Boston, U.S.A., was definitely higher than in London.

In pregnancy the volume of the blood is increased and the increase of plasma is greater than that of cells. Keith, Rowntree and Geraghty[14] showed that the increase of blood amounted to 300 or 400 c.c. at the end of pregnancy, and that the total haemoglobin was not increased in proportion. Diekmann and Wagner[15] found that the blood-volume increased 16 per cent by the 13th week and 23 per cent towards term; the rise in plasma volume was a little greater, 18 per cent and 25 per cent. The observations were made on 13 patients and this rise was present in all but one. After the 26th week there was very little change. The maximal decrease in haemoglobin concentration, which occurred between the 26th and 35th weeks, was 15 per cent, but the total haemoglobin in the body increased by 13 per cent. Thomson *et al.*[16] found that the increase in blood and plasma volume reached a maximum in the 9th month. Strauss and Castle[17] believe that the physiological anaemia of pregnancy is a hydraemia, and that a reduction of body haemoglobin only occurs in the last 3 months with defective diet or defective absorption from anacidity. Oberst and Plass[18] in a

study of plasma protein concentration and blood-water reached a similar conclusion. Feldman *et al.*[19] followed the cell-volume, haemoglobin, refractive index, and water-content of the blood and showed that dilution developed in the course of the first 130 days and was fully established by 220 days. It is agreed, therefore, that there is a fall in haemoglobin concentration in preg-

TABLE V.

Recent Literature on Haemoglobin in Pregnancy.

Authors	Region	Number observed	Mean haemoglobin	Method	Notes
			Gm. / 100 c.c.		
Lyon,[21] 1929 ...	New York	200	13.0	Sahli	Many in first and second pregnancies.
Galloway,[22] 1929 ...	Chicago	382	11.35	Sahli	Third trimester only. 48 per cent primigravidae.
Davidson, Fullerton, and Campbell,[23] 1935	Aberdeen	819	10.8	Haldane*	Very poor.
Mackay,[24] 1935 ...	London	109	11.52	Haldane*	In institute for unmarried.
Smallwood,[27] 1936 ...	Birmingham	106	10.5		At term.
Boycott,[25] 1936 ...	London	222		Haldane*	Moderately poor. 25 per cent under 11 grams.
Oberst and Plass,[18] 1936	Iowa	20	11.69	O_2 capacity	10 primigravidae. Third trimester.
Adair, Dieckmann, and Grant,[31] 1936 ...	Chicago	7835	11.56	Newcomer*	At lying-in hospital.
		170	11.79		Private patients.
Bethell,[34] 1936 ...	Ann Arbour	28	11.85	Sahli*	Cases with qualitatively normal blood only.
Reid and Mackintosh[28] 1937	Stockport	1108		Haldane	Fifty-four per cent under 11.8 grams. Ten per cent under 9.7 grams.
Ramsay, Thierens and Magee,[32] 1938 ...	Blackburn	95	12.45	Dare	Antenatal clinics.

* Standard checked by observer.

nancy, which is due, at least partly, to dilution of the blood; which is fully established by the 26th week; and which does not indicate an anaemia. The series reported here concerns the period of pregnancy in which this dilution is fully established, and it shows the absence of a constant rise or fall in haemoglobin concentration after the 26th week.

Bland, Goldstein and First,[20] and Dieckmann and Wagner give a summary of the results of earlier investigations into the haemoglobin level in pregnancy. The results of recent investigations are given in Table V. From this it will be seen that the mean of the present series, 12.4 grams, is a little higher than has been found by most other observers.

Parity. Lyon,[21] Galloway,[22] Bland, Goldstein and First, Mackay,[24] Boycott,[25] Fullerton[26] and Rao were unable to show that the number of pregnancies was related to the haemoglobin level. Studies of iron balance (Fullerton) suggests that the saving of iron due to the absence of menstruation more than compensates for the iron losses due to the foetus, labour and lactation, in fact there is an economy of iron during pregnancy. There is thus not any reason why parity should depress the iron and haemoglobin stores, and Fullerton suggests that it has a favourable influence. But the menstrual loss in women who have borne children is greater than in those who have not, and we suggest that this is an important factor in accounting for the difference which we found between primigravidae and multiparae and for the fact that subsequent pregnancies did not affect this difference. Often, however, the coming of the first baby makes a fundamental change in the life the mother leads. There are additional expenses and demands on her time and energy which may keep her indoors and prevent her leading so hygienic an existence as was possible before. This penalty of motherhood would be prolonged, but not necessarily intensified, by subsequent children, and would be a factor telling against multiparae in general. Our result agrees with that of Oberst and Plass who found that the mean haemoglobin of primigravidae was 0.5 grams higher than that of multiparae.

Age. Fullerton describes a gradual fall in the haemoglobin level throughout the reproductive period of a woman's life and a rise after the menopause; his patients were extremely poor. Smallwood[27] describes a similar cycle. Mackay, Boycott, and Rao could not show that age had any relation to anaemia in pregnancy. Reid and Mackintosh[28] found that anaemia was more frequent in older primigravidae than in younger if the economic

factor was adverse. So few of our subjects were over 30 years of age that we have not any evidence to present as to the incidence of anaemia in later life. We think that age alone has no adverse effect on the haemoglobin level in the first half of reproductive life, and anaemia seems to become less frequent. Our figures for primigravidae agree with those of Mackay in showing the highest level in the later twenties.

Economic status. It has been pointed out that poor economic circumstances tell particularly heavily on the nutrition of the mother. Her need of iron is greater than that of her menfolk, but the custom is for these to receive the pick of the rations, and if anyone is to go short it is not they and not the children. That poverty is, in fact, associated with anaemia in pregnancy is not so firmly established as might be expected. Boycott could not correlate income with incidence of anaemia and quotes the figures of Balfour and Drury[29] for Tyneside women which showed only a slightly greater tendency to anaemia among the poorest. Moore and Pilman-Williams[30] state that at the Royal Free Hospital antenatal clinic the women with small incomes had less haemoglobin than the others, but they do not give the data. Bland, Goldstein and First found the haemoglobin level under 10.3 grams in 62 per cent of their private patients and 80 per cent of their hospital patients. Adair, Dieckmann and Grant[31] give the mean haemoglobin of 7835 hospital patients as 11.56 and of 170 private patients as 11.79. Reid and Mackintosh found the incidence of anaemia was greater in women from families with less than 12 shillings per head and particularly so in the case of multiparae. If we compare series with series, we find the highest mean haemoglobin in that of Lyon, noted as better working-class excluding chronic disease, in that of Ramsay, Thierens and Magee[31] from the Blackburn antenatal clinics, and in Adair, Dieckmann and Grant's private patients. Bethell's[32] series is not comparable for cases of anaemia were excluded. The lowest means are those of Davidson, Fullerton and Campbell, whose subjects were in extreme poverty, and of Smallwood, for women attending antenatal clinics in Birmingham. Bland, Goldstein and First state that their patients were poor and more or less underfed; in 80 per cent of them the haemoglobin was less than 10.3 grams. It seems that the poorest communities tend to a low haemoglobin level and to a high incidence of anaemia.

Our results show that, although a haemoglobin level under 11 grams occurred more often in our sample of coloured women receiving less than 10 shillings per week per head than among the

rest, and although the mean haemoglobin was a little lower, neither of these differences was significant. They also show that there was no difference between the poorer section of the Europeans and the coloured. But the mean haemoglobin level of the Europeans receiving £1 and more was significantly greater than that of the poor Europeans and than that of the coloured, and the occurrence of haemoglobin levels under 11 was significantly less frequent.

It is, therefore, suggested that there is an adverse nutritional factor affecting all the coloured and the poorer Europeans. The coloured, as a whole, have a lower income than the poorer section of the Europeans but their mean haemoglobin is not lower; this may be due to a larger proportion of the coloured income being spent on food, to a more fortunate selection of the foods consumed, and to greater assistance from charity.

Widdowson and McCance[33] found that the addition of iron to the diet increased the haemoglobin of all their female subjects by an average of 10 per cent, whereas it had no effect on the men. Their subjects were of the middle class. If this improvement can be effected in women living under good conditions it is not surprising that less fortunate women show a greater degree of anaemia, and it is probable that the routine administration of iron during pregnancy would be of value to most of the women of the poorer classes. That such an improvement can, in fact, be made, has been shown by Moore and Pillman-Williams in London and by Smallwood in Birmingham.

Summary.

The haemoglobin concentration in the blood of 213 European and coloured women attending an antenatal clinic in Cape Town has been studied during the last 3 months of pregnancy.

The mean concentration was 12.40 grams per 100 c.c. with standard deviation 1.055. The mean concentration was not different in the two communities, did not vary with time during the period of pregnancy studied, and was probably not influenced by age below 30 years.

The mean concentration was lower in multiparae, and this is attributed to their greater menstrual loss.

The mean haemoglobin of the Europeans receiving more than £1 per week per head of family was higher than that of those receiving less and than that of the coloured, nearly all of whom received much less. The incidence of low haemoglobin levels was greater in the latter groups.

The routine administration of iron is suggested as a safeguard against this form of malnutrition.

We wish to express our thanks to Professor E. C. Crichton for allowing us to make this study on his patients, to Professor B. J. Ryrie for his interest in this work, and to Mr. E. J. Duncan who did a large share of the collection of specimens and laboratory work.

REFERENCES.

1. Van Slyke, D. D., and J. M. Neill. *Journ. Biol. Chem.*, 1924, lxi, 523.
2. Hufner, G. *Arch. Anat. Physiol.*, 1894, p. 130. Quoted from Peters and Van Slyke[10].
3. Bradford Hill. "Principles of Medical Statistics." Lancet Ltd., London, 1937.
4. Tippett, L. H. C. "The Methods of Statistics," Williams and Norgate Ltd., London, 1931, p. 80.
5. Fisher, R. A. "Statistical Methods for Research Workers." Oliver and Boyd, Edinburgh, 1938, p. 177.
6. Haldane, J. S. *Journ. Physiol.*, 1901, xxvi, 497.
7. Price-Jones, C. *Journ. Path. and Bact.*, 1931, xxxiv, 779.
8. Dor, M., and A. Lambrechts. *C. R. Soc. Biol., Paris*, 1938, cxxvii, 1121.
9. Heilmeyer, L. "Medizinische Spektrophotometrie," Fischer, Jena, 1933, p. 71.
10. Peters, J. P., and D. D. Van Slyke. "Quant. Clinical Chemistry," Vol. I. Ballière, Tindall and Cox, London, 1931, p. 544.
11. Sokhey, S. S. "Report of Haffkine Institute, 1929," p. 26. Quoted from Price-Jones[7].
12. Rao, M. V. R. *Indian Journ. Med. Res.*, 1938, xxv, 957.
13. Wintrobe, M. M. *Arch. Int. Med.*, 1930, xlv, 287.
14. Keith, N. M., L. G. Rowntree, and J. T. Geraghty. *Arch. Int. Med.*, 1915, xvi, 547.
15. Dieckmann, W. J., and C. R. Wagner. *Arch. Int. Med.*, 1934, liii, 71 and 188.
16. Thomson, K. J., A. Hirsheimer, J. B. Gibson, and W. A. Evans. *Amer. Journ. Obstet. and Gynecol.*, 1938, **xxxvi**, 48.
17. Strauss, M. B., and W. B. Castle. *Amer. Journ. Med. Sci.*, 1932, clxxxiv, 663.
18. Oberst, F. W., and E. D. Plass. *Amer. Journ. Obstet. and Gynecol.*, 1936, xxxi, 61.
19. Feldman, H., E. C. Van Donk, H. Steenbock, and E. F. Schneiders. *Amer. Journ. Physiol.*, 1936, cxv, 69.
20. Bland, P. B., L. Goldstein, and A. First. *Amer. Journ. Med. Sci.*, 1930, clxxix, 48.
21. Lyon, E. C. *Journ. Amer. Med. Assoc.*, 1929, xcii, 11.
22. Galloway, C. E. *Journ. Amer. Med. Assoc.*, 1929, xciii, 1695.

23. Davidson, L. S. P., H. W. Fullerton, and R. M. Campbell. *Brit. Med. Journ.*, 1935, ii, 195.
24. Mackay, H. M. M. *Lancet*, 1935, ccxxviii, 1431.
25. Boycott, J. A. *Lancet*, 1936, ccxxx, 1165.
26. Fullerton, H. W. *Brit. Med. Journ.*, 1936, ii, 523.
27. Smallwood, W. C. *Brit. Med. Journ.*, 1936, ii, 573.
28. Reid, W. S., and J. M. Mackintosh. *Lancet*, 1937, ccxxxiii, 1389.
29. Balfour, M., and J. Drury. "Motherhood in Special Areas of Durham and Tyneside," London, 1935, p. 25. Quoted from Boycott (25).
30. Moore, J., and E. M. Pillman-Williams. *Brit. Med. Journ.*, 1936, ii, 528.
31. Adair, F. L., W. J. Dieckmann, and K. Grant. *Amer. Journ. Obstet. and Gynecol.*, 1936, xxxii, 560.
32. Ramsay, J., V. T. Thierens, and H. E. Magee. *Brit. Med. Journ.*, 1938, i, 1199.
33. Widdowson, E. M., and R. A. McCance. *Journ. Hygiene*, 1936, xxxvi, 13.
34. Bethell, F. H. *Journ. Amer. Med. Assoc.*, 1936, cvii, 564.

Royal College of Obstetricians and Gynaecologists

The quarterly meeting of the Council was held in the College House on Saturday, July 22nd, 1939, with the President, Professor W. Fletcher Shaw, in the Chair.

Professor William Fletcher Shaw, M.D., F.R.C.P., Hon. F.A.C.S., was re-elected President; Eardley Lancelot Holland, M.D., B.S., F.R.C.P., F.R.C.S., and Miles Harris Phillips, M.D., B.S., F.R.C.S., Hon. M.D., were elected Vice-Presidents.

The following officers were also elected:

John Prescott Hedley, M.A., M.B., M.C., F.R.C.P., F.R.C.S., Honorary Treasurer; Aleck William Bourne, M.A., M.B., Ch.B., F.R.C.S., Honorary Curator of Museum; Frederick Roques, M.A., M.D., M.Ch., F.R.C.S., Honorary Librarian; George Frederick Gibberd, M.B., M.S., F.R.C.S., Honorary Secretary.

The following Member was admitted to the Fellowship:—

Douglas Hamilton MacLeod, London.

and the following were admitted to the Membership:

John Lyle Cameron, London
William Melville Capper, Bristol
Anthony Charles, London
Alice Eleanora Dickie, London
Charles McTaggart Hopkins, Australia

The following were elected to the Membership:

Russell Ian Ritchie, New Zealand
Bruce Hunter Anderson, Melbourne
Alexander Wilson Andison, Canada
George Wills Blomfield, Leeds
David Robinson Cairns, London
William David A. Callam, Edinburgh
Gilbert Dalley, London
Donald Stewart Greig, London

Thomas Neville Hart, Bolton
William Hawksworth, New Zealand
William Morton Lemmon, Melbourne
George Gordon Lennon, Birmingham
Frank Haighton Lord, Melbourne
Ruvin Lyons, Canada
Thomas Alistair MacFarlane, New Zealand
David Matthew W. Maxwell, Windsor
Shivaprasanna Misra, Calcutta
Charles Victor Salisbury, Sydney
Everall Mary Shippam, London
Richard de Soldenhoff, Lyme Regis
Ebenezer A. Thomas, Vellore, India
Geoffrey Benion Thomas, Lahore
Sydney Lance Townsend, Melbourne
John Dickie Watt, Romford
Ella Windeyer, Sydney.

HOSPITAL REPORTS

MEDICAL AND CLINICAL REPORT OF THE EDINBURGH ROYAL MATERNITY AND SIMPSON MEMORIAL HOSPITAL, 1938.

Edinburgh presents us with an excellent contribution to obstetric knowledge, prepared with every indication of care and thoroughness, and provided with a list of contents which would do justice to any textbook.

In the course of the year 855 patients were delivered in their own homes and 2392 patients were treated in hospital. Of the 2392 patients admitted 21 died in hospital: this represents a mortality of 8.7 per 1000. In addition 5 cases were transferred to the City Fever Hospital, raising the total number of deaths to 26. The final mortality figure is, therefore, 10.8 per 1000, which rather suggests that the climate of Edinburgh must have changed since our last visit, because this figure approaches that of many hospitals which are situated in the tropics. Nevertheless, when we examine the report more thoroughly we find that our first impressions are false, and one cannot help but think that the data might have been placed before us in a manner better chosen to impress. We now see that of the 1520 booked patients delivered in hospital, 5 died, giving a mortality rate of 3.2 per 1000, which is definitely in keeping with the average figures for this country. Of the 638 non-booked patients delivered in the hospital 9 died, giving a mortality of approximately 14 per 1000. A little reorganization of this preliminary paragraph would have done much to relieve our unwarranted fears.

The order in which this report is presented statistically is a little out of the ordinary, but the sub-classification has obvious advantages and must have caused the author many a headache in the course of its preparation. The statistical portion of the report commences with abnormal labour, the sub-heading being contracted pelvis; this is followed by sections dealing with twins, occipito-posterior positions of the vertex, breech presentations; and thereafter behaves as any other obstetric report. This is one of the few reports from hospitals in this country in which an unusual method of presenting the material is adopted.

The results of breech presentation were of the following order: total number of cases, 92, the general still-birth rate was 43.5 per cent. The still-birth rate among booked primiparae was 43.5 per cent, but the usual error relating to small numbers creeps in here.

There were 20 cases of eclampsia of which one patient died: 2 were treated by Caesarean section. Severe albuminuria of pregnancy occurred in 181 patients, giving an incidence of approximately 8 per cent: details of individual cases are not provided, but a *résumé* of the methods of treatment used is attached to this section.

The department dealt with 49 cases of cardiac disease complicated by pregnancy; there were 2 maternal deaths in this group.

Rupture of the uterus occurred on 4 occasions, there was one maternal death. Full notes of 3 of these cases are given on page 49.

The forceps-rate for 1938 was 13 per cent.

Caesarean section was performed on 52 occasions, the maternal mortality being 1.9 per cent: unfortunately the records do not give an indication of the relative popularities of the classical and lower segment operations.

The report also includes a summary of the work done in the district, and short notes on the maternal deaths which occurred in the hospital and after transfer to the City Fever Hospital.

A paediatric section is included; in addition to the usual contents this section contains interesting data on the correlation of maturity and causes of death, the incidence of intracranial haemorrhage, the relation between maturity and abnormal labour and the death-rate of premature infants.

In spite of the slight deviation from the usual type of report it is felt that this is an excellent production, and that the Registrar should be complimented on the care and patience which he has exhibited in providing these statistics.

Barton Gilbert.

NATIONAL MATERNITY HOSPITAL, DUBLIN: CLINICAL REPORT, 1938.

This is a voluminous report of approximately 100 pages; we therefore approached it with considerable trepidation and were relieved to find that it is not so formidable as its outward appearance would lead us to believe. This is in part due to the method of presentation and the spacing adopted by the printer: many pages contain the records of only 4 or 5 cases which is due in practically every case to the information contained in the remarks column.

The principal event of the year as far as the National Maternity Hospital was concerned was the completion of the final section of the hospital, which was reached at the end of November. The completed hospital can contain 145 patients. During 1938 the maternity department delivered 2568 patients. The incidence of albuminuria was extraordinarily high, since it is reported that 491 patients suffered from this condition.

The total number of deliveries by the forceps was 192, giving an incidence of 7.5 per cent. The total number of deaths among patients admitted to the hospital was 18 which corresponds to a mortality rate of 7 per 1000.

Two unusual cases are reported; one was a patient who developed a thrombosis of the left popliteal artery which resulted in gangrene of the leg below the knee, and the other was a patient who was operated upon 12 years ago for a vestibular anus. This patient was admitted in labour with a breech presentation, the vagina being very short and the cervix low. Two fibrous bands extended from the back of the symphysis to the level of the

third piece of the sacrum, leaving a small opening which would admit only two fingers. The bands proved an absolute obstruction to the descent of the foetus, and Caesarean section was necessary to deliver the patient.

The general order of this report follows the approved form and is very well cross-referenced.

There were 123 cases of breech presentation, but the table which is provided does not give us at a glance the foetal mortality rates for the breech presentation. On calculating from the available figures it appears that this figure is 25 per cent for all primiparae and about 15 per cent for all multiparae. These figures are quite respectable and we cannot see why they have not been given at the head of the table just like the others, some of which are not of much interest. This hospital has one of the largest series of breech presentations and it seems a pity not to give all the available data on this page. External cephalic version appears to have been performed on only 6 occasions if we are to go on the information furnished on page 10 of the report. Not finding any other details we must assume this to be true and conclude that external version must be regarded as an unsatisfactory method of dealing with the breech in this hospital. This will also account for the large number of breech deliveries carried out during 1938.

Twelve cases of eclampsia occurred in the practice of this hospital, and four of the patients died. All the patients were treated conservatively. The term eclampsism is employed frequently in this report; in the other reports which we have examined this word has not appeared, probably indicating its redundancy.

Details are given of 67 cases of uterine inertia, these should prove useful to anyone who wishes to investigate this condition. Induction of labour is dealt with very thoroughly, the details of 140 successful cases being given. It would also be interesting to know the number of cases in which it was unsuccessful and how often it was necessary to repeat medical induction. Information with regard to the former is to be found 24 pages down the book after the commencement of this section!

The forceps-rate was about 7.5 per cent, and one finds by a little arithmetic that the foetal death-rate associated with delivery by the forceps was approximately 9 per cent.

The end of the report is occupied by a summary of the work of the extern maternity department and the gynaecological departments. The total number of patients operated upon in the gynaecological department was 557. Ten of the admissions into the gynaecological department were suffering from carcinoma of the cervix, one of these patients died on the fourth week after the insertion of radium.

Wertheim's operation was practised on three occasions, but no further details are given concerning these cases of carcinoma of the cervix.

The gynaecological report occupies only 2 pages compared with 92 for the maternity section, and it is to be hoped that in future more details will be available concerning the gynaecological material, especially concerning cancer of the genital tract.

Barton Gilbert.

140TH. ANNUAL REPORT OF THE SOCIETY OF THE LYING-IN HOSPITAL OF THE CITY OF NEW YORK, 1938.

It is unnecessary to say that we feel very pleased that the Lying-in Hospital has honoured us with the presentation of a copy of the Annual Report. This is an institution the history of which dates back to 1799 when it was first incorporated and facilities opened to patients on August 1st of that year. In 1801 the hospital inaugurated courses of instruction in midwifery for men medical students, and was probably the first institution to do so in America. From this time the hospital has never ceased to carry out its work, but has increased its sphere of usefulness by providing financial assistance to patients confined in their own homes, inaugurated a scientific publication, became affiliated with the Cornell University Medical College, and finally moved to its new site in 1932.

In the course of 140 years of life it has trained more than 10,000 doctors. During the early days of its existence the maternal death-rate was approximately 40 per 1000; this has now been reduced to just a little more than 2 per 1000.

Dr. James A. Harrar, formerly chief surgeon to the hospital, published during 1938 an important historical contribution on the History of the Lying-in Hospital.

Turning the pages of the report we see a picture of one of the delivery rooms, and a picture of the new "blood bank." The bed in the delivery room is no wider than an ordinary operating table, which seems a little unusual, unless all American women have operative deliveries.

Several pages are given to nursing activities, the ladies auxiliary society and to the social service department after which we come to the statistics of the obstetrical and gynaecological departments.

In 1938, 3,622 obstetrical patients were treated in the hospital and a further 671 in an adjacent wing. The total number of maternity patients, including ectopic pregnancies and abortions, was 4,271. The maternal mortality was 4 deaths in this number, or 1.04 per 1000 pregnancies.

It is not clear from the records whether a test for syphilis was made as a routine, but it is recorded that the incidence is not less than 2.85 per cent. The term toxaemia, 260 cases, is employed to include acute yellow atrophy, chronic nephritis, low reserve kidney, pre-eclampsia, eclampsia and a group labelled unclassified, including 89 cases. The incidence of all these conditions is 8.2 per cent, but the figure means little to us because our interpretation of the word toxaemia is not the same, and moreover one third of the cases are unclassified.

The incidence of delivery by the forceps is 12.6 per cent which is about twice that of teaching institutions in this country. The incidence of Caesarean section is 2.64 per cent which is also higher than the average in the British Isles. The total number of stillbirths and neonatal deaths was 111 giving a gross infantile mortality of 3.06 per cent, which is very low.

During 1938, 1,289 patients were admitted to the gynaecological department: 351 of these were submitted to major operations and 727 had minor

operations performed upon them. There were 8 deaths, giving a gross mortality of 0.62 per cent.

This report makes interesting reading from both the medical and social points of view, and we trust that we shall be favoured with a copy of the 141st report when it is published.

Barton Gilbert.

ROYAL MATERNITY HOSPITAL, BELFAST.

Registrar's Report.

This is the Report for 1938. In addition to the units for clean cases, the Hospital is provided with the Rea Block, which is employed for the treatment of potential, suspect, and established forms of sepsis. The majority of admissions to this block are emergency cases, the patients suffering from established sepsis. Mr. McClure points out at the beginning of the report that these emergency admissions have not been included in estimating the maternal mortality rate: all other abnormalities are included in the appropriate tables.

In order to prevent overcrowding in the wards admission has been refused to multiparae attending the antenatal department, unless some abnormality of pregnancy was found. From this it follows that there must have been a proportional rise in the number of abnormal cases.

An interesting table appears on page 6, giving the maternal mortality from 1932 to 1938. In 1932 the total admissions were 954 and the mortality rate was 1.7 per cent: in 1938 the admissions had risen to 1,944 and the mortality rate had fallen to 0.92. The mortality rate for patients attending the hospital's antenatal department was 3.1 per 1,000 for 1938, which is about the average for the whole country.

The case records of the maternal deaths are the best which have been inspected in recent reports, and should form a model for those who wish for a guide when constructing a maternity report. It is needless to say that the standard of a report not only depends upon the medical organizer but upon the clerical service which is placed at his disposal. Some registrars are expected to take the quill and the office-stool and remain in lonesome retirement in order to prepare a report, while others are expected to conduct the clinics, teach, and wait in operating theatres, and at the end of the day find they have an hour to spend on their report when clerical assistance is no longer available. One cannot help but feel that the Royal Maternity Hospital of Belfast is very fortunate in having both a registrar with an orderly, scientific mind and a well-organized clerical department.

The tabular report begins in a rather unusual way, but one finds from the survey of a number of reports that great hospitals often have idiosyncracies in this direction. After the usual preamble, the popular form of report commences with the tabulated results of the various presentations.

The Belfast report table IV, which immediately follows maternal morbidity, deals with eclampsia, and this is followed by sections dealing with heart disease, prolapse of the umbilical cord, face and brow presentation, multiple pregnancy, and breech delivery. This order seems a little irregular, since it does not appear to follow any of the usual lines of thought such as order of commonness, or chronological order. Nevertheless, with regard to the section on eclampsia in which there are 11 cases, all the patients were treated by Strogonoff's method, and all were cured.

Cardiac disease caused considerable concern; there were 37 cases in all; of these patients 21 were delivered by the natural forces, only one mother died. Mitral stenosis accounted for 30 of the total cases.

Prolapse of the umbilical cord occurred on 20 occasions, the foetal mortality being 50 per cent.

Under the heading of breech deliveries we are provided with some interesting information which is worth reproducing: the total number of breech presentations was 83. The corrected foetal mortalities are: in primiparae, 13.04 per cent; in antenatal primigravidae, 5.88 per cent; in emergency primiparae, 33.33 per cent; in multiparae, 26 per cent; in antenatal multiparae, 20.51 per cent; in emergency multiparae, 45.45 per cent. It is an obvious biological statistical error to calculate percentages to two places of decimals with a total number of 83 cases. We are quite content with the figures preceding the decimal point, and conclude that Belfast is the place for every primigravida, in whom the foetus presents by the breech, to have her baby. The high figures for multiparae are associated with other factors such as placenta praevia.

Table X reveals that there were 40 cases of posterior position of the occiput. One imagines that this means that only 40 of the 1,944 admissions caused any trouble because the occiput was posterior. There must have been many more posterior positions of the vertex at the onset of labour, but the report does not contain a note of the various presentations so we are unable to calculate the percentage of occipito-posterior positions of the vertex which failed to rotate. Of the 40 cases mentioned half required manual rotation and delivery by the forceps.

Caesarean section was performed on 60 occasions; the classical operation was performed 11 times, and the lower segment operation 49 times. The maternal mortality was 6.66 per cent.

Five complete pages are occupied by the records of induction of abortion, miscarriage, and premature labour, and page after page reveal the indication to be toxaemia of pregnancy. Since this condition seemed to be such an important clinical entity we have hunted through the report for the tabulated details of this condition but have failed to find them. The value of this report would have been much enriched by the inclusion of toxaemia records. We were particularly anxious to note the average time of onset and to estimate the time which elapsed before delivery took place, but it cannot be obtained from the material which is presented.

The foetal mortality is of the following order: 1,406 babies were born

during the year, and of these 112 were still-born, giving a stillbirth-rate of nearly 8 per cent.

This report, which bears every indication of great labour, is, generally speaking, good, but could be improved by a few small additions as outlined above.

Barton Gilbert.

RIGSHOSPITALETS FODEAFDELING B OG GYNAEKOLOGISKE AFDELING M.

OBSTETRIC REPORT BY PROFESSOR D. E. HAUCH, COPENHAGEN, 1938.

The following is a brief résumé of Professor Hauch's report:

Admissions to hospital	1,880
Maternal deaths	16
Grand total of deliveries	23,633

Of the number admitted 1811 were delivered, and 1853 babies were born. Of these 1111 were primigravidae, and 700 were multiparae.

Eclampsia.

There were 13 cases of eclampsia. Maternal deaths, 1; stillbirths, 5. (There were also 2 maternal deaths from the toxic state).

Placenta praevia.

There were 15 cases of placenta praevia (all varieties). Maternal deaths, 2; stillbirths, 9.

In 3 cases the placenta was completely praevia, and in 12 it was partial.

Accidental ante-partum haemorrhage.

Total number of cases, 34; maternal deaths, 2; stillbirths, 17.

Prolapse of the cord.

There were 18 cases. Maternal deaths, 0; stillbirths, 7.

This is followed by a comprehensive account of the various obstetric operations. It is interesting to note that out of 114 cases of forceps delivery, Kjellands forceps were favoured in 88. The scalp forceps is also employed in certain patients suffering from uterine inertia.

Induction of labour.

Induction of labour was performed on 46 occasions: in this series there were 3 maternal deaths, and 10 stillbirths. The important indications were of the following order: nephritis, 17; obstetric disproportion, 11, toxaemia, 3.

Anaesthetics in labour.

The number of patients who are provided with deep anaesthesia is striking as will be seen from the following table:

Chloroform	828	to the obstetric degree
Ether	18	
General ether anaesthesia	54	
General chloroform anaesthesia ...	228	
Chloroform and ether	11	
Ethyl chloride	26	
	1165	

Intravenous anaesthesia was given 434 times.

Episiotomy.

Episiotomy was performed on 309 occasions. Complete perineal tears occurred on 4 occasions.

Manual removal of the placenta.

Manual removal of the placenta, 10; manual removal of cotyledons, 7. Seven of these patients had a febrile puerperium, and 1 died.

Puerperal mortality and morbidity.

Puerperal sepsis, mortality, 0.11 per cent; puerperal morbidity, 18.1 per cent (339 patients); puerperal morbidity, under 1 day's fever, 12.7 per cent (235 patients).

In the detailed list of puerperal morbidity it is noticed that about one-fifth of the cases are due to engorgement or mild mastitis.

Babies.

The number of babies born was 1853. Of these 1281 were born at full-time, 524 were premature, and there were 48 abortions.

The neo-natal death-rate for all babies was 6.9 per cent.

Maternal deaths.

The 16 maternal deaths were due to the following causes: puerperal sepsis 2, placenta 2, eclampsia 3, shock and anaemia 1, pulmonary embolism 2, nephritis 2, nephritis and cerebral haemorrhage 1, heart disease 1, bronchopneumonia 2.

This is followed by a report on the gynaecological operations performed in association with the work of the department.

Dr. Hauch is to be congratulated on the work of his department, and we thank him for his kind thought in despatching a copy of his report to this journal.

Barton Gilbert.

BOOK REVIEWS

"Clinical and Pathological Gynaecology," by J. THORNWELL WITHERSPOON, M.A., M.D. Publisher: Henry Kimpton, London. Pages: 373, illustrated with 271 engravings. Price 30s.

The author is to be congratulated on the production of this book which contains so much useful knowledge, embodying as it does the essential anatomy, physiology, biochemistry and general medicine relevant to gynaecology.

It appears that the original instigation to write the book came from teaching a course which was termed "Clinical Pathological Gynaecology," for want of a better name, from which the present production obtains its title. The author very definitely states that it is not to be regarded as a textbook, but as an introduction to clinical pathological gynaecology. The text is not complete, as it avoids all discussion of embryology and congenital abnormalities. Clinical methods of examination and operative technique are not discussed: these are intentional omissions, and do not detract from the value of the book, which is primarily intended for the medical student in order that he may acquire a sound knowledge of gynaecological pathology and its relation to clinical states.

This book should find a well-deserved place in the libraries of American medical students, but from the point of view of the student who intends to pass his examinations in this country it is not particularly suitable. As an example of the difficulty which a British student may encounter the following may be given:—under the heading of chronic hypertrophic ulcerative vulvitis one finds syphiloma, elephantiasis, esthiomene, and rodent ulcer included. All these lesions, including rodent ulcer, are regarded as having a common fundamental aetiology. In this country we employ the term rodent ulcer in a very different way, and it is felt that if a student presented an examiner with the American use of this term it might quite reasonably be regarded as unsatisfactory.

The book is well illustrated by 271 black and white pictures, many of which are microphotographs: they are printed on good paper which gives excellent definition except under the higher magnifications, but this is a common failing of high magnification reproductions in black and white.

It is felt that in this country the book would be most useful to housemen rather than to students, since the former are more capable of appreciating its contents, and have no longer to fear the examiner who may not be familiar with American nomenclature.

In summary we feel that the author and publishers are to be congratulated on the material and preparation of this book.

B.G.

"Midwifery for Nurses," by HENRY RUSSELL ANDREWS, M.D., F.R.C.O.G., and VICTOR LACK, M.B., F.R.C.O.G. Publishers: Messrs. Edward Arnold and Co. Price, 6*s*.

In this, the eighth edition, the authors state that considerable alterations have been made to cover the syllabus of the first part of the training under the new regulations of the Central Midwives' Board. As in other editions we find the teaching sound and concise, and although the subject is dealt with rather superficially, as in the treatment of prolapse of the umbilical cord, the authors rather imply that the knee-chest position is only of use in cord presentation, which does not correspond with the usual teaching, and on page 144 the causes of ante-partum haemorrhage, associated with, but not due to the pregnancy, such as cervical erosion or polypus are not mentioned. It should, nevertheless, be a useful first textbook for the pupil midwife at the beginning of her training. The book is well tabulated, and extremely well produced. Some excellent illustrations by Miss Barclay Smith add considerably to its value. Figure 19, a section of the placenta, and Figure 21, the foetal circulation, will be especially appreciated by pupil midwives.

M. Sparkes.

"The Childless Family: Its Cause and Cure," by EDWARD F. GRIFFITH, M.R.C.S., L.R.C.P. First edition (Kegan Paul, Trench and Co., Ltd.), 128 pp.; illustrated. Price, 3*s*. 6*d*. net.

THIS little book is divided into six chapters, the first of which contains a short review of the early history of sterility, reference being made to some of the magical rites and religious ceremonies of India and China which are associated with supposed cure.

The second chapter gives a short description of the reproductive organs, while a third deals with the male and female hormones. Special reference is made to the importance of Leydig's cells in the production of the testicular hormone as also to the various functions of that body.

The aetiological factors of permanent and temporary sterility are reviewed in the fourth chapter, while the fifth deals entirely with those which are responsible for the production of sterility in the male, including oligospermia, immaturity and abnormal secretions.

The concluding chapter is devoted to investigation and treatment. A brief, but much-needed, warning is given regarding the misuse of hormones.

An excellent series of X-ray photographs is included in this chapter to illustrate the use of lipiodal injection of the Fallopian tubes in diagnosis and treatment.

The author points out that childlessness is often a source of great unhappiness and matrimonial discord, and indicates that the purpose of his book is to consider as simply as possibly some of the main problems involved, and to explain the meaning of recent scientific discoveries directed to a cure of a condition too often regarded as inevitable.

We think the author has presented his subject in a clear and interesting manner, and has justified his object.

J.McG.

"Aids to Gynaecological Nursing," by HILDA M. GRATION, S.R.N., S.C.M., D.N. Publishers: Baillière, Tindale and Cox. Price 3s. 6d.

In this, the fourth of the Nurses' Aids Series, the author, in her preface, states that the book is designed chiefly for the use of student nurses during their training in a general hospital, and she offers no apology for the simplicity of the text. "As most teachers learn by experience that it is better to teach less, and to try to teach first principles simply and thoroughly," Miss Gration may be congratulated on the amount of information she has given so concisely.

Excellent line drawings add to the book's appeal to the student nurse; there is an excellent table showing the position and function of the endocrine glands. Ante- intra- and post-natal care is well described, but in Fig. 18 the diagrams are too small to be of value.

Chapter viii, dealing with the venereal diseases and the nursing care required should be of the greatest value to both student nurses and certified midwives. The precautions essential in hospital to prevent the spread of infection are especially well described. The various gynaecological conditions are defined, and the operation for each, including post-operative care. Complications which may occur, and the duties of the nurse, are given in great detail. The various positions of the patient for gynaecological treatments, and the instruments used in gynaecology, are illustrated.

This is a very useful book, and can be recommended to both the student and the qualified nurse.

M. Sparkes.

"The Physiology of Anaesthesia," H. K. BEECHER, M.D., Instructor in Anaesthesia, Harvard Medical School, 388 pp. Price, 17*s*. 6*d*. (Oxford University Press).

THE author states that he has attempted to describe the response of the body to anaesthetic agents and to anaesthesia: to discuss the *rationale* rather than the practice of anaesthesia. We congratulate Dr. Beecher on the admirable way in which he has succeeded in this task.

The subject matter is clearly and concisely dealt with, his arguments are well stated and his conclusions are sound, the book showing evidence of being the result of a large amount of painstaking research and review of the literature on the subject. It is a book that no anaesthetist can afford to leave unread, and we welcome Dr. Beecher's book as a step forward in the sorely needed rationalization of anaesthesia.

G. C. Steele.

Review of Current Literature.

Director: FREDERICK ROQUES, M.A., M.D., M.Chir. (Cantab.), F.R.C.S., F.R.C.O.G.

THIS Review contains the lists of contents and abstracts of the more important articles from the following journals with which the "Journal of Obstetrics and Gynaecology of the British Empire" exchanges:—

British.—The Lancet; British Medical Journal.

Canadian.—The Canadian Medical Association Journal; Bulletin Médical de Quebec.

Australian.—Medical Journal of Australia; The Australian and New Zealand Journal of Surgery.

Indian.—The Calcutta Medical Journal.

American.—American Journal of Obstetrics and Gynecology; The Journal of the American Medical Association; Surgery, Gynecology and Obstetrics; American Journal of Diseases of Children.

French.—La Gynécologie; Gynécologie et Obstétrique; Bulletin de la Société d'Obstétrique et de Gynécologie de Paris.

Belgian.—Brûxelles Médical.

Italian.—Annali di Obstetrica e Ginecologia; Archivo di Obstetrica e Ginecologia; Revista Italiana di Ginecologia, Bologna.

German.—Archiv für Gynäkologie; Zeitschrift für Geburtshülfe und Gynäkologie; Zentralblatt für Gynäkologie; Monatsschrift für Geburtshülfe und Gynäkologie; Münchener Medizinische Wochenschrift; Monatsschrift für Krebsbekampfung.

Scandinavian.—Acta Obstetrica Scandinavica.

South American.—Boletin de la Sociedad Obstetrica y Ginecologia de Buenos Aires.

Japanese.—Japanese Journal of Obstetrics and Gynaecology.

The Review of Current Literature thus keeps the readers of the Journal in touch with current literature throughout the world. At the end of the year an Index of all the subjects contained in the articles of the above journals is printed. Arrangements are also made to include abstracts of important articles on border-line subjects, such as Physiology, Biology, and Biochemistry.

LIST OF ABSTRACTORS

London: J. BEATTIE, F.R.C.S.; A. C. BELL, F.R.C.S.; R. K. BOWES, F.R.C.S.; J. LYLE CAMERON, F.R.C.S.; ALBERT DAVIS, F.R.C.S.; F. H. FINLAISON, F.R.C.S.; B. GILBERT, F.R.C.S.; R. J. KELLAR, F.R.C.S.; R. LIGHTWOOD, F.R.C.P.; J. A. MOORE, F.R.C.S.; C. D. READ, F.R.C.S. (Edin.); F. ROQUES, F.R.C.S.; R. WINTERTON, F.R.C.S.

Felsted: W. E. CROWTHER, M.B.

Leeds: R. H. B. ADAMSON, M.D., AND B. JEAFFRESON, F.R.C.S.

Liverpool: M. DATNOW, F.R.C.S.; P. MALPAS, F.R.C.S.; T. N. A. JEFFCOATE, F.R.C.S.

Manchester: R. NEWTON, M.D.

Glasgow: JANE H. FILSHILL.

British Medical Journal.

November 26, 1938, No. 4064.

*Administration of pituitary extract in the third stage of labour. G. W. Blomfield.

December 17, 1938, No. 4067.

*The xenopus pregnancy test. E. R. Elkan.

January 14, 1939, No. 4071.

*Treatment of sterility. M. Moore White.

February 11, 1939, No. 4075.

*Intra-uterine aspiration. Bela Lorincz and Albert Davis.

April 1, 1939, No. 4082.

*Induction of labour. Eileen C. Wise.

Administration of Pituitary Extract in the Third Stage of Labour.

Two series of over 1,000 cases of labour were observed by the author; in one 1 c.c. of pituitrin or pitocin was given in the third stage, in the other this was omitted. In both the post-partum blood loss was measured, and the result of this experiment shows that there is apparently no danger in giving the drug in the third stage of labour. The amount of haemorrhage is, apparently, not much affected. It appears, therefore, that previous misgivings are unfounded, and that in specific cases pitocin may be usefully and safely employed.

The Xenopus Pregnancy Test.

The xenopus pregnancy test has now been in operation long enough in this country to give a fairly accurate estimate of its value. One hundred and fifty tests have been carried out on 742 toads, and only 8 of the latter died during the course of the tests. This is a great advantage, as the animals are not cheap and require care to breed. With regard to its reliability, the test would appear to be equal with the Friedman and Aschheim-Zondek reactions. It has the great additional advantage of allowing the diagnosis of pregnancy to be made within 24 hours, and is also comparatively easy to carry out.

Treatment of Sterility.

Of 62 sterile women, 17.7 per cent showed blocked Fallopian tubes on both sides, in 19 per cent on one side. All women had been sterile for 2 to 11 years; of those in whom the tubes were patent and the husband fertile, 47.8 per cent became pregnant within a period of 1 to 7 months after treatment. This treatment consists in the administration of moderate doses of oestrin, but

these results were somewhat vitiated by the fact that pregnancy following simple lipiodol salpingography or air insufflation is not uncommon.

INTRA-UTERINE ASPIRATION.

An apparatus is described which allows of the aspiration of small pieces of endometrium to be used in the diagnosis of various gynaecological conditions. These include ectopic gestation, incomplete abortion, sterility, etc. The apparatus may be used without an anaesthetic and in the consulting room, and is an effective substitute for diagnostic curettage in many cases.

INDUCTION OF LABOUR.

Induction of labour by combined surgical and medical methods was carried out in 287 cases. The method was to give small doses of quinine in the three weeks previous to delivery, larger doses being given on admission. Castor oil and an enema were also prescribed and 5 days later the membranes were artificially ruptured anteriorily. The average duration of labour was 16 hours in the primigravidae and 8 hours in the multiparae, these times comparing favourably with the corresponding number of cases in which labour was allowed to begin spontaneously. In the great majority of cases labour began within 24 hours, and no failures were recorded. There was apparently no increase in the forceps-rate, and no increase in the foetal mortality. There were no maternal deaths.

A. A. Davis.

The Canadian Medical Association Journal.

Vol. xl, No. 6, June, 1939.

*The effect of cervical secretions on the vitality of spermatozoa. Melville C. Watson, M.B.

THE EFFECT OF CERVICAL SECRETIONS ON THE VITALITY OF SPERMATOZOA.

The detrimental effect of vaginal and cervical fluids on spermatozoa is an important causative factor in sterile marriages. A fresh alkaline secretion from the cervical glands into which spermatozoa may pass from the seminal fluid greatly favours their powers to fertilize the ovum.

The author has made numerous examinations of cervical secretions obtained after coitus to determine the number of actively motile spermatozoa present. He found deficient cervical secretion, tenacious mucous plugs in the cervix and a few pus cells indicating a mild vaginal inflammation. All of these conditions are unfavourable to spermatozoa.

Acting on the assumption that the administration of oestrogenic substances, which stimulate secretion from the glands of the genital tract, would do much to remedy these abnormalities, he treated a small series of patients, during the estimated fertile period, with 100,000 to 150,000 international units of

oestradiol benzoate intramuscularly. All these patients before treatment were afflicted in some degree with the conditions described, and examination of each showed very few actively motile spermatozoa on three successive post-coital examinations made at intervals of 48 hours. Examination after treatment revealed an increase in quantity and a change to normal viscosity and transparency of the cervical secretion. There was also a noted increase in the number of actively motile spermatozoa, not only in the vicinity of, but also at a distance from, the cervix, up to four hours after coitus.

He is, therefore, of the opinion that the administration of oestrogens, such as oestradiol benzoate, oesteriol glucuronide, or progynon B. are very useful remedies in the treatment of sterility associated with the conditions just cited, when other abnormalities are absent.

J. Lyle Cameron.

American Journal of Obstetrics and Gynecology.

Vol. xxxvi, No. 1.

Dystocia in diabetes insipidus. C. Fisher, H. W. Magoun and S. W. Ranson.

The histologic correlation of endometrial and cervical biopsies. Anthony Wollner.

The causes of vaginal bleeding and the histology of the endometrium after the menopause. Howard C. Taylor, Jr., and Robert Millen.

A chemical test for pregnancy applied to the determination of oestrin in the urine of normal and toxaemic patients in the last trimester of pregnancy. J. E. Savage, H. Boyd Wylie and L. H. Douglass.

Studies on the circulation in pregnancy. K. J. Thompson, A. Hirsheimer, John G. Gibson and William A. Evans.

Pregnancy and tuberculosis. Edwin M. Jameson.

The effect of oestrogenic hormone upon the contractility of the Fallopian tubes. Samuel H. Geist, Udall J. Salmon and Maurice Mintz.

The non-protein, urea, and rest nitrogen of the blood during labour and the puerperium. J. F. Cadden and Arthur M. Faris.

Gynaecological features of carcinoma of the large bowel. Joseph Schwartz and Harry Bergman.

*Pitocin in the third stage of labour. Milo R. White.

Vaginectomy. James C. Masson and Paul A. Knepper.

The bilirubin liver function test in the toxaemias of pregnancy. Robert A. Lyon.

*The potential bisexual character of the ovary. Andrew J. Ramsay and James F. McCahey.

*Virilism and female pseudohermaphroditism with relation to the bisexual nature of the ovary. James F. McCahey and Andrew J. Ramsay.

An evaluation of the anterior pituitary-like substance intradermal test for pregnancy. Joseph J. Friedman and Harold Fink.

Uterine bleeding with virilism. Virginia G. Rheuby.

Arsenical encephalitis during pregnancy. Conrad Kuehn, R. A. Keating and E. von Haam.

Actinomycosis and blastomycosis of female genitalia. Morris Joseph and F. Summerhill.

A five-year study of eclampsia in Maryland. J. Morris Reese and Frank W. Peyton.

Erythroblastosis. Louis M. Hellman and Arthur T. Hertig.

Puerperal gangrene of the extremities. Paul E. Gutman.

True knot of umbilical cord causing foetal death before labour. Hugh B. McNally.

Gangrene of the extremities in puerperal thrombo-phlebitis. John H. Tilley.

Lipoma of the uterus associated with carcinoma. Arthur A. Humphrey and Russell L. Mustard.

A manikin for individual student use. J. Bay Jacobs.

Treatment of premature separation of the placenta. P. Brooke Bland and A. E. Rakoff.

Society transactions.

Selected abstracts. Sterility.

Vol. xxxvi, No. 2.

The experimental production of ovulation in the human subject. M. Edward Davis and Arthur K. Koff.

A study of the water, sodium, and energy exchange during the latter part of pregnancy. R. H. Freyberg, R. D. Reekie and C. Folsome.

One-stage operation for resection of the recto-sigmoid and rectum for carcinoma (with or without hysterectomy). J. P. Pratt.

*Further observations on the role of streptococcus in so-called trichomonas vaginalis vaginitis. G. F. Hibbert and F. H. Falls.

A consideration of artificial fever therapy and sulphanilamide therapy in the treatment of gonorrhoeal infections of women. L. M. Randall, Frank H. Krusen and Edwin G. Bannick.

Artificial fever therapy in pelvic inflammatory disease. Milton A. Darling, James M. Berris and Max Newman.

*Effect of quinine upon the auditory nerve. Ray A. West.

Sterilization of obstetric patients in Vanderbilt University Hospital, 1925–1937. G. S. McClellan and Lucius E. Burch.

A study of 288 primiparae over the age of 35 compared with 300 primiparae under the age of 25. Charles E. Galloway and Tom D. Paul.

Pelvic measurements of 4,144 Iowa women. W. F. Mengert.

Management of placenta praevia. David Findley.

An analysis of a human ovotestis. J. R. Reinberger and C. S. Simkins.

Intraligamentary pregnancy. Phillips K. Champion and Nicola J. Tessitore.

Observations on intra-uterine pressure during the first stage of labour. Joseph P. Salerno.

Cystic endometrial changes in ovulatory cycles. Leo Wilson and Raphael Kurzrok.

Full-time abdominal pregnancy with recovery of both mother and baby. William D. Crecca and R. A. Cacciarelli.

Editorial Comment.
A survey of 447 maternal deaths occurring in the Counties of Maryland during the years 1930 to 1936, inclusive. C. H. Peckham.
Society transactions.
Collective review. The pathology of the ovarian hormone.
Selected abstracts. Physiology of pregnancy.

Vol. xxxvi, No. 3.

*Foetal respiration in relation to atelectasis and intra-uterine pneumonia. Franklin F. Snyder and Morris Rosenfeld.
Visceral allergy. James R. Goodall and R. M. H. Power.
Weight changes and toxaemia of late pregnancy. R. S. Siddall and H. C. Mack.
Unsuspected tuberculosis in pregnant women as revealed by routine Roentgenological examinations. C. Wesley Eisele and Elwood W. Mason.
An evaluation of the sedimentation test in the differential diagnosis of acute pelvic inflammatory disease and acute appendicitis. Charles Lintgen and Kenneth Fry.
*The management of breech delivery. Roy W. Mohler.
The cold pressor test in pregnancy. W. J. Dieckmann, Herbert L. Michel and Paul W. Woodruff.
Heart disease complicating pregnancy. Henricus J. Stander.
The problem of infant mortality. Joshua Ronsheim.
Infant mortality at the Cook County Hospital among sixteen thousand deliveries. David S. Hillis and S. J. Benensohn.
The activation of uterine muscle by oestrin and its relation to uterine growth. Samuel R. M. Reynolds.
Surgical treatment of dysmenorrhea. James C. Masson and Rosemary Shoemaker.
The safety and advantages of office curettage. S. Leon Israel and Charles Mazer.
Rupture of the Graafian follicles. Joseph T. Smith.
*Hyperemesis gravidarum. J. E. Fitzgerald and Augusta Webster.
*Relation of oral thrush to vaginal mycosis and the incidence of each. Paul W. Woodruff and H. C. Hesseltine.
Pulmonary tuberculosis in an active obstetric service. Leslie H. Tisdall.
A study of 738 cases of uterine bleeding in conditions other than pregnancy. Fred Weintraub.
Hyperpyrexia produced by the hot box in combination with the Elliott treatment. W. Spencer Gurnee.
Hyperemesis gravidarum. M. Alex Novey and C. L. Goodhand.
Maternal intracranial haemorrhage complicating labour. H. Leo Moskowitz and H. Schneider.
Krukenburg tumour complicating pregnancy. Henry T. Hagstrom.
The pathological properties of meconium. W. H. Rubovits, E. Taft and F. Neuwelt.

Sepsis puerperalis thrombo-phlebitica putrida, Schottmuller's syndrome. Oscar H. Bloom.

Aplasia of the lower female genital tract. C. A. Elden.

Segmental torsion of Fallopian tube in a young virgin. Samuel A. Wolfe and David Kuperstein.

Melanoma of the vulva. R. Charles Nucci.

Carcinoma of the cervix during pregnancy. Samuel Goldstein.

Torsion of the Fallopian tube. Sanford Kaminester.

Atresia of the vagina. Joseph L. Baer.

A case of secondary abdominal pregnancy. Craig W. Muckle.

A pessary for moderately-sized cystoceles. Cheney M. Stimson.

The intravenous administration of post-pituitary extract for obstetric purposes. J. Hofbauer.

The thyroid gland and pregnancy. Robert D. Mussey.

Selected Abstracts—Puerperium.

Vol. xxxvi, No. 4.

*Carcinoma of the cervix. Norman F. Miller and Clair E. Folsome.

*The relation of the pituitary gland to the menopause. Benjamin P. Watson, Phillip E. Smith and Raphael Kerzrok.

*The relative value of pure oxygen and of carbon dioxide mixtures in experimental resuscitation. N. J. Eastman, R. B. Dunn and Joseph Kreiselman.

The placental transmission of neoarsphenamine in relation to the stage of pregnancy. Franklin F. Snyder and Harold Speert.

The diet of the pregnant woman. E. V. McCollum.

*Rhythmic changes in the skin capillaries and their relation to menstruation. John I. Brewer.

Unpredictability of the phenomena accompanying the menstrual cycle in normal women. Julius E. Lackner, Hans Wachtel and Samuel Soskin.

The geographical distribution and effect of climate on eclampsia, toxaemia of pregnancy, hyperemesis gravidarum, and abruptio placentae. William J. Dieckmann.

Congenital absence and traumatic obliteration of the vagina and its treatment with inlaying Thirsch grafts. Virgil S. Counseller.

The dilating bag in obstetrics. Edward G. Waters.

A ten-year study of Caesarean section in the St. Louis Maternity Hospital. S. D. Soule.

A comparison of the end-results of treatment of endocervitis by electrophysical methods: cautery, coagulation, and conization. Adolph Jacoby.

The effect of sodium lactate in raising the carbon-dioxide combining power in the toxaemias of pregnancy. Leon C. Chesley and Felix H. Vann.

Hormonal bio-assay in a case of ovarian disgerminoma. Frank Spielman and Frank L. Morton.

An X-ray study of gastric function during labour. A. Hirsheimer, D. A. January and J. J. Daversa.

Granulosa cell tumours of the ovary with precocious puberty. John Parks.
Granulosa cell tumour of the ovary. Eugene H. Countiss.
Status of the thecoma and its relation to the granulosa cell tumour. J. P. Greenhill and Robert B. Greenblatt.
Primary giant granulosa cell tumour of retroperitoneal origin with development into the mesosigmoideum. Walter W. Voigt.
The treatment of late abdominal pregnancy. A. Charles Posner.
Endometrial hyperplasia (puberty), adeno-carcinoma, fifteen years' follow-up. Vincent P. Mazzola.
An unusual ovarian cyst. Harry M. Nelson.
Gangrenous vulval oedema necessitating Caesarean section. Richard Torpin and Robert Battey Crichton.
Unilateral absence of the Fallopian tube and ovary. Daniel R. Mishell.
Vesico-vaginal fistula repaired with rustless steel wire. Henry D. Furniss.
A scissor type cervical biopsy punch. Harry O. Maryan.
Editorial. Syphilis and pregnancy.

Pitocin in the Third Stage of Labour.

There is probably, in the whole of obstetrics, no question so vexed as that of whether pituitrin should be given before the end of the third stage or not. In this paper White gives his experience of 630 patients to whom pitocin was administered before the birth of the placenta. The drug was given intravenously in 505 cases, and in 125 cases it was given intramuscularly because difficulty was experienced in passing the needle into a vein. So as to be sure that the drug was given at the beginning of the third stage, the arm was prepared before the birth of the child. After removing 2 to 3 c.cs. of blood to dilute the pitocin, the mixture was injected slowly over a period of one minute. All blood lost was collected in a basin and the placenta was expressed from the vagina in every case as soon as it was evident that it had left the fundus. He found that the administration of pitocin had no undesirable systemic effect and that the drug induced a prompt and uniform contraction of the uterus, which hastened the separation and the expulsion of the placenta without any increase in the incidence of retention. He also found that the results of the intravenous method were better than those of the intramuscular method, both as regards the total loss of blood and the time of complete separation. Shock was noted in only one case in the whole series. Although this occurred in a patient with a toxaemia who had received the drug intravenously, the author is of opinion that pitocin is not contra-indicated in cases of toxaemia as the pressor hormone is absent.

The Potential Bisexual Character of the Ovary.

Ramsay and McCahey advance the theory that the sex gland in every embryo is essentially bisexual and that it is never indetermined, as it is usually considered to be, in the very early stages of development. They give an account of the changes involved in the development of a testis

and an ovary from the original genital fold, and they explain that it is apparent that the gonads of all embryos are identical. If a testis is to be formed, then there is no radical alteration in the original structure plan; but if an ovary is to be formed, there is a secondarily superimposed addition of cortical tissue from the surface germinal epithelium upon the centrally placed primary gonad. Thus they affirm that the gonad is primarily male and that the female condition is a secondary one. According to this theory, the authors state that probably in all ovaries some retention of cells of the original gonad, which are capable of exhibiting degrees of male characteristics, will be found. To test this idea, they examined many ovaries which were removed at autopsy from normal women. They found that the rete ovarii were present in the lateral half of the hilus of the ovary in every case and in 70 per cent of the specimens it was attached to the tubules of the epoöphoron by its extension into the mesovarium. They also regularly found groups of epithelioid cells, very similar to the interstitial cells of the testis, intimately related to the rete ovarii groups. When present in increased numbers they were scattered throughout the hilus, and even into the mesovarium. In the ovary of one woman of 34 years, who showed signs of virilism, they found a number of epithelial cords which were most similar to the testicular cords of the primitive testis.

VIRILISM AND FEMALE PSEUDOHERMAPHRODITISM WITH RELATION TO THE BISEXUAL NATURE OF THE OVARY.

In this paper the same authors discuss the causes of virilism and pseudohermaphroditism. They believe that these two conditions are related and that the former is the adult form of masculinization and that the latter is the foetal type of the same phenomenon. They do not agree with Meyer that the primary gonad, which is common to both sexes, is composed of physiologically indifferent cells, as such a theory would mean that a condition of potential hermaphroditism exists during the early stage of gonadal development in every embryo. They believe that the primary gonad in both sexes is testicular in nature; that in the male it develops into a testicle and that in the female the cortex of the ovary arises from other cells which grow around the primary gonad. The finding of testicular hormone in the urine of the normal female is another indication that the human ovary is bisexual in nature. In cases of virilism and hermaphroditism an excess of this hormone has been found. Their explanation of the presence of male hormone in the normal female urine is a question of utilization and that the amount excreted in the female is the complete amount secreted by vestigial testicular remains in the ovary.

If the theory of these authors in these two papers is correct, then difficulty will be experienced in explaining the origin of the disgerminoma but, on the other hand, it might be possible to locate and remove the causal active testicular remains in the ovary in cases of virilism and hermaphroditism.

FURTHER OBSERVATIONS ON THE ROLE OF STREPTOCOCCUS IN SO-CALLED TRICHOMONAS VAGINALIS VAGINITIS.

Hibbert and Falls are of the opinion that too much stress has been made concerning the part played by the trichomona as the causative agent in vaginitis, and they believe that a specific strain of streptococcus is of the greater importance. Thus they agree with Craig and Faust, and also with Dobell, that a true trichomona infection cannot take place in a normal host. This opinion of theirs is of the utmost importance if this type of vaginitis is to be correctly treated and they substantiate their claim to this opinion by some experimental work on women and by certain observations of their own clinical cases. In 19 of their cases they have found the parasite regularly and yet these patients show no evidence of vaginitis and repeated smears fail to demonstrate the streptococcus in question. Again, they have proved that the trichomona can still be found in cases which have been made symptom-free by their own methods. They also maintain that they have frequently seen cases of vaginitis, typical of that produced by the trichomonad, and yet they have failed to demonstrate this parasite. Because of these findings they believe that there is a causative agent other than the trichomona, which may produce the typical clinical syndrome. However, they acknowledge the possibility of a symbiotic relation between the trichomonad and the streptococcus or an individual immunity for one or both of these organisms.

The organism isolated from their cases was identified as the streptococcus sub-acidus of Holman. They inoculated the cervix of five normal women with a pure culture of this organism and they were successful in producing definite vaginitis in four of them. This vaginitis was completely cleared up by the local application of a broth filtrate of the organism and the intradermal injection of a standardized vaccine of the same organism. Their series of cases of trichomona infections were treated in exactly the same way and they managed to get 63 out of 84 gynaecological and obstetrical cases symptom-free for a period of three months after treatment.

EFFECT OF QUININE UPON THE AUDITORY NERVE.

In this paper West brings forward the disquieting suggestion that the employment of quinine as a means of inducing labour may give rise to a permanent defect of the auditory nerve in the child. He quotes evidence in the literature that quinine has a selective action on the eighth nerve, that the drug is carried through the placental circulation and reaches the foetus in high concentrations, and that certain cases of child deafness have been attributed to the administration of quinine to the mother.

To prove this the author carried out experiments on 12 rabbits. After administering quinine for 10 days one animal was killed and its auditory nerve was removed and examined. In this animal, which had received 5 grains of quinine bisulphate by direct administration by mouth, every

fibre of the nerve contained minute black granules of degenerated fat globules. The remaining 11 animals were from three different litters, the mothers of whom had received 5 grains, 3 grains and 1 grain of quinine respectively. Even in the offspring of the mother which received only 1 grain of the drug, degenerative changes were found in the spirale ganglion, the auditory nerve and the vestibular nerve. As the degeneration in the ganglion was less severe than that of the nerve fibres the author came to the conclusion that probably the myelinated nerves were affected first. Again, as every individual of each litter of animals showed the same degenerative changes in the auditory nerve, he does not think that it can occur only in individuals who have an idiosyncrasy to quinine, as some obstetricians think.

FOETAL RESPIRATION IN RELATION TO ATELECTASIS AND INTRA-UTERINE PNEUMONIA.

While considering the problem of asphyxia neonatorum, atelectasis and pneumonia of the stillborn, Snyder and Rosenfeld came to the conclusion that it was essential to determine the normal state of activity of the respiratory system of the foetus before birth. Experiments to stimulate the foetus of the rabbit *in utero* under general anaesthesia failed; but when the need of anaesthesia was abolished by section of the lumbar cord, the foetûs within the uterus were seen to be breathing actively. Rhythmical excursions of the chest wall and diaphragm continued throughout periods of observation lasting many hours. They found that intra-uterine failure of respiration could be classified under the three headings of (a) anoxaemic, (b) acapneic and (c) anaesthetic: and that, therefore, prevention of asphyxia of the newborn was centred in the period preceding birth.

They also came to the conclusion that atelectasis and pneumonia could be traced to pathological complications of normal intra-uterine respiration. By their experiments, and by their investigations of the lungs of the foetus they proved that the alveoli are fully formed and partially dilated before air respiration takes place, and they believe that the presence of amniotic fluid in the lungs is a normal consequence of foetal respiration.

Although the lungs are filled with amniotic fluid at the time of birth, they explain that the foetus is not drowned because adequate aeration is promptly provided. Since the elasticity of the alveolar walls permits an increase in size of the alveoli of such magnitude, the surface area now obstructed by fluid becomes relatively greatly reduced.

Because of these findings it is evident to them that the breathing of abnormal amniotic fluid, containing debris of excessive amount or of abnormal type, may result in injury of the lungs before birth; obstruction of the bronchioles may lead to atelectasis, and contamination of the amniotic fluid by irritant substances, like meconium or bacteria, may cause intra-uterine pneumonia.

THE MANAGEMENT OF BREECH DELIVERY.

Mohler reports the results of 709 consecutive breech deliveries and gives an account of the principles which, he believes, should be strictly adhered to in all cases.

In this series the incidence was 4.7 per cent for approximately 18,000 cases; 295 patients were primiparae and 414 were multiparae. The gross foetal mortality was 186, about 26 per cent. The corrected foetal mortality of 5.5 per cent was obtained after the subtraction of 147 babies which were lost because they were premature and non-viable or deformed, so that the type of presentation was not responsible for their deaths.

He feels that the important points in the management of breech presentation are, (a) an X-ray study, late in the pre-natal period, to determine the relative size of the foetus and pelvis; (b) that it is safer to deliver a larger than average-sized child by Caesarean section; (c) that all breech babies should be delivered by the vagina, under light anaesthesia, after the breech has been delivered, and that this should always be done by an adequately trained person who understands the normal mechanism; (d) that all impacted breech presentations should be delivered under deep surgical anaesthesia after full dilatation of the cervix has taken place; if delivery is essential before full dilatation, he recommends manual dilatation before extraction, or, preferably, Caesarean section; (e) that the forceps should always be used after the head has become engaged.

HYPEREMESIS GRAVIDARUM.

The authors report the results of treatment of 360 women admitted for pernicious vomiting; 29 of these were re-admitted, one or more times, for a recurrence of symptoms. Less than one-third of these could be classified as severe cases as their stay in hospital extended beyond 10 days. Immediately after admission all cases were treated by the administration of fluids to counteract the dehydration consequent upon the vomiting. In most cases this was given in the form of 5 per cent glucose into the rectum. Nothing was given by mouth for 24 hours. In other cases rectal salines were deemed enough. Under such forms of treatment prompt improvement took place and the authors maintain that admission to hospital, with the complete banning of all visitors, is usually all that is necessary. In the more severe types, additional fluid was administered, either as 5 per cent glucose subcutaneously or a 25 per cent solution intravenously.

Fifteen patients died; the pregnancy was interrupted in 9 of these cases. The pregnancy was also interrupted in 23 other cases, all of which recovered. The authors believe that many of these deaths could have been avoided by emptying the uterus sooner. They stress the importance of the early recognition of cases which are not going to improve and especially those cases in which the vomiting ceases but there remain persistent tachycardia, elevated temperature and persistent urine

abnormalities. In 6 of the 15 fatal cases the patients were retaining food for some time before death. If it is decided to terminate the pregnancy, they strongly advise vaginal hysterotomy rather than the introduction of cervical packs, bags, etc.

In the discussion which followed the reading of this paper, Falls pointed out that a certain number of these patients show evidence of hyperthyroidism as shown by a basal metabolic rate of +110 to +140. In such circumstances he has been able easily to control the vomiting with 10 drops of Lugol's solution three times a day.

THE RELATION OF ORAL THRUSH TO VAGINAL MYCOSIS AND THE INCIDENCE OF EACH.

During the investigation of some cases of oral thrush in the newborn, Woodruff and Hesseltine came to the conclusion that there was an association between this condition and the presence of fungi in the vagina. They found that the incidence of fungi in the vagina of women during the last three months of their pregnancy was 28 per cent. Out of 14,640 live births 90 had oral thrush, an incidence of 0.6 per cent. Out of 47 births from mothers known to have vaginal mycosis, 10 babies had oral thrush, an incidence of 21 per cent. Therefore, the authors maintain that a baby born of a mother contaminated with vaginal mycosis has approximately a 35 times greater chance of developing oral thrush than a baby born of a normal mother.

CARCINOMA OF THE CERVIX.

In this paper Miller and Folsome give a very good account of the treatment of 676 cases of cancer of the cervix, collected from the State of Michigan from 1931 to 1937 inclusive. They describe how the general condition of the patients and the local extent of their growth is thoroughly investigated before their attendance at a conference whose members are composed of the gynaecologists and representatives from the departments of Roentgenology and pathology. At this conference the treatment was worked out and, while treatment in general followed accepted precepts, they did not attempt to treat every patient in exactly the same way. Seventy-six per cent were treated with combined X-rays and radium; 10 per cent, being advanced cases, received X-rays only; 11 per cent were treated by other methods or combinations; and three per cent had no treatment of any kind.

Their results did not differ much from the average; 24.42 per cent in the six-year group, and 23.66 per cent in the five-year group representing the survival rate. Because of this they are of the opinion that even with this new and vastly improved therapy, the very nature of cancer makes its complete destruction, without costly damage to normal tissues, an impractical likelihood except in early cases.

Their investigations have impressed upon them the need of a six-month physical examination of every woman over 35 years of age rather

than to depend upon educating the lay public to recognize the symptoms of an early growth, as initial symptoms do not necessarily imply that the growth is early. They recommend a new clinical classification of six groups which corresponds to the League of Nations grouping, except that groups I and IV are each subdivided into two. They end this paper on a rather pessimistic note concerning the value of radium. With the eight-year, ten-year, and fifteen-year follow-up reports of the pioneers in this field comes the growing suspicion that what is good for the late case is not necessarily good for the early case and they feel that, in this small minority of early cases, a return to surgery of adequate character is highly desirable.

THE RELATION OF THE PITUITARY GLAND TO THE MENOPAUSE.

The menopause may be due to the failure of the anterior pituitary gland, the failure of the end-organs, the uterus, cervix, etc., or to the failure of the ovaries. Watson and his co-workers believed that it is due to a failure of the ovaries to respond to the gonadotropic hormones, as large quantities of follicle-stimulating hormone can always be found in the urine and because the symptoms of the menopause may be present without amenorrhoea.

In order to prove this fact they treated a series of 11 patients of all ages with massive injections of gonadotropic hormone (Antex-Leo), just prior to an abdominal section for retroversion, fibroids or some other uterine abnormality. So far as they could judge, there was no ovarian or adnexal disease present at the time of the injections. They describe the macroscopic and microscopic findings of the ovaries at the time of operation of each case and they noted that the younger the ovaries the more definite was the response to the hormone stimulus. Three patients aged 25 showed a response in both ovaries. In one patient aged 26 there was a response only in one ovary. In two patients aged 34 and 37, respectively, there was only a slight response in both ovaries, and in the remaining four patients, aged between 43 and 67 years, there was no response at all. In all the cases that reacted there were no normal follicles but multiple follicular cysts were present, with degeneration of the granulosa cell layer.

They came to the absolute conclusion that the menopause is due to a loss of response on the part of the ovary to gonadotropic hormones.

THE RELATIVE VALUE OF PURE OXYGEN AND OF CARBON DIOXIDE MIXTURES IN EXPERIMENTAL RESUSCITATION.

So as to decide upon the relative value of these two methods of resuscitation in asphyxia neonatorum the authors performed a series of experiments on dogs. By making them breathe 100 per cent nitrous oxide, they obtained a condition of apnoea which reduplicated the clinical picture, as well as the blood oxygen levels, of asphyxia neonatorum. Atfer breathing had ceased for approximately 30 seconds, artificial respiration was instituted with a

Kreiselman resuscitator, various gas mixtures being used. From the point of view of time when breathing was re-established, they found that there was very little difference between the use of pure oxygen and 10 per cent or 25 per cent of carbon dioxide in oxygen. But when the length of apnoea was prolonged to 60 seconds, pure oxygen was much quicker in re-establishing respiration. They also found that the respiration re-established after pure oxygen was regular and was sustained without any further artificial respiration; whereas that resulting from the inhalation of a carbon dioxide mixture was irregular and convulsive and the apnoea tended to recur. As a 25 per cent carbon dioxide mixture is often recommended for the treatment of asphyxia neonatorum and used for long periods, the authors tried the effect of such a gas. They found that this inhalation for 7 to 15 minutes gave rise to toxic effects which resulted in death in many of their experiments.

In their summary, they come to the conclusion that pure oxygen is more efficacious, safer and more rational than any form of carbon dioxide-oxygen mixture.

RHYTHMIC CHANGES IN THE SKIN CAPILLARIES AND THEIR RELATION TO MENSTRUATION.

As menstruation is fundamentally a vascular phenomenon Brewer studied the peripheral vascular changes, produced by capillary bleeding, throughout the cycle. The capillary haemorrhage was brought about by an instrument exerting a negative pressure upon an area of the skin of the antecubital fossa. Fifty-five normal healthy working girls, between the ages of 19 and 50, were studied. In 40 of these the menstrual cycle was within the variations of normal and in 15 the cycle was abnormal; the abnormality being classified as functional amenorrhoea, post-climacteric amenorrhoea, functional bleeding, pregnancy amenorrhoea, etc. In the normal cases an increase of capillary fragility was clearly demonstrated during the first two days of menstruation; at the same time a moderate premenstrual increase was noted. The change in the negative pressure needed to cause the capillary bleeding occurred very rapidly and was most marked during the first two days of menstruation; During the inter-menstruum, the negative pressure remained fairly constant but there were numerous instances when there was a brief period of increased fragility near the mid-point of the cycle. In a case of functional uterine bleeding this capillary fragility was completely dissociated with the losses. The author is of the opinion that these capillary changes are consequent upon a vascular spasm. He gives a short description of the evidence on this point and describes the capillary fragility reaction obtained experimentally after the subcutaneous injection of a small dose of adrenalin solution in one female and seven males. He obtained an exactly similar chart during the blanching effect of the drug as he obtained during menstruation. This paper is well worth reading in detail.

Bryan Jeaffreson.

The Journal of the American Medical Association.

Vol. cxi, No. 22, November 26, 1938.

Marriage among mental defectives. Charles P. Sheldon and Lloyd H. Ziegler.
Photography of the uterine cervix. Charles E. Galloway.
Reopening ligated uterine tubes by uterine insufflation with carbon dioxide. I. C. Rubin.
Ganglioneuroma of the ovary. Harry C. Schmeisser and W. A. D. Anderson.
Asphyxia of the newborn. Editorial.

Vol. cxi, No. 23, December 3, 1938.

Peripheral neuritis due to sulphanilamide. A. M. Ornsteen and William Furst.

Vol. cxi, No. 25, December 17, 1938.

*Pathology of the placenta. R. A. Bartholomew.

Vol. cxi, No. 26, December 24, 1938.

The cervix uteri in obstetrics and gynecology. Joseph L. Baer.

Vol. cxii, No. 1, January 7, 1939.

Action of doses of 800 kilovolt Roentgen rays on carcinoma of the uterine cervix. Henry Schmitz, H. E. Schmitz and J. F. Sheehan.

Vol. cxii, No. 3, January 21, 1939.

Chronic cervicitis. W. T. Black.
Regulation of serum calcium during pregnancy. Meyer Bodansky and Virginia E. Duff.

Vol. cxii, No. 5, February 4, 1939.

Infection of the immature vagina. Goodrich C. Schauffler, Reinhold Kanzler and Caroline Schauffler.

Vol. cxii, No. 19, May 13, 1939.

*Treatment of vulvo-vaginitis with oestrogen. Charles Mazer and Fred R. Shechter.

Vol. cxii, No. 23, June 10, 1939.

Maternal mortality. E. F. Daily.
Corpus luteum cystoma. Homer Wheelon and Gale Wilson.

Vol. cxii, No. 24, June 17, 1939.

*Pelviradiography and clinical pelvimetry: comparative values in the prognosis of the outcome of labour. Emanuel M. Rappaport and Samuel J. Scadron.

Vol. cxii, No. 25, June 24, 1939.

The relief of pain in childbirth. Editorial.

Vol. cxiii, No. 1, July 1, 1939.

*Sulphanilamide in puerperal infections due to clostridium Welchii. Joseph F. Sadusk and Constantino P. Manahan.
Vulvo-vaginitis in pregnancy. E. G. Waters and Eakle W. Cartwright.
Pathology of obstetric shock. Editorial.

REVIEW OF CURRENT LITERATURE

Pathology of the Placenta.

This paper deals mainly with the causation of placental infarcts, and their bearing with regard to the toxaemias of pregnancy. It is suggested that infarction is a result of changes in the foetal rather than the maternal vessels, and results in part from the high blood-cholesterol content and in part to trauma to the vessels occasioned by foetal movements. Infarction may occur suddenly or gradually, the appearance of the various transitional types being described. The author believes that the size, number and acuteness of the infarcts have an important bearing on the severity of the toxaemic condition which he suggests arises secondarily to the infarction. Toxaemia may arise from the absorption into the maternal circulation of poisonous split protein products of placental autolysis, these probably consisting of peptone, histamine and guanidine. The eclamptogenic character of placental autolysate is explained by the high content of arginine in placental tissue, from which guanidine may be obtained.

The author found that by examining a series of unknown placentae he was able in 90 per cent of cases to diagnose correctly that pre-eclampsia, eclampsia or abruptio placentae had occurred.

Treatment of Vulvo-vaginitis with Oestrogen.

In the treatment of gonococcal vaginitis of children with oestrogen, the principle aimed at is to secure a cornification of the vaginal epithelium, and to reduce the *p*H of the secretions to six or less. In the present series of cases oestrogen was administered by three routes: orally, hypodermically and by vaginal suppositories. Oral therapy was unsuccessful, and the best results were obtained by local application. In patients treated by vaginal suppositories the oestrogen dosage required was less than in those who received injections, with a consequent reduction in the occurrence of side effects such as enlargement of the breasts, growth of pubic hair, and premature menstruation.

The importance of thorough treatment is insisted upon, a full eight weeks being the optimum.

Pelviradiography and Clinical Pelvimetry.

Three hundred and fifty patients were subjected to X-ray pelvimetry, the time selected being 10 days before the expected date of delivery. Of the pure types of pelvis thus disclosed the gynaecoid was the most common, followed by anthropoid, android and platypelloid in that order. Many pelves fell into intermediate types of which the android-gynaecoid was the most common. It was found that X-ray pelvimetry usually gave larger measurements than had been arrived at by clinical examination, and was of especial use when contracted pelvis was suspected.

The greatest use of the method lay in assessing the relation between the foetal head and the pelvic inlet, being less successful in giving the measurements of the outlet. X-ray examination will give information on such points

as the subpubic angle and length of rami, the angle of the sacrosciatic notch, the inclination of the sacrum, the position of the ischial spines, and the angle of the pelvic side walls, and such knowledge may be of importance in predicting the outcome of labour in doubtful cases.

SULPHANILAMIDE IN PUERPERAL INFECTIONS DUE TO CLOSTRIDIUM WELCHII.

Two cases of post-abortional clostridium Welchii infection are reported, in both of which hyperpyrexia was present, and the organisms were grown from the lochia and blood. Treatment consisted in massive doses of sulphanilamide, with rapid recovery in each instance.

The authors tested the action of sulphanilamide on clostridium Welchii *in vitro*, and found that the drug inhibited growth of the organism, its action being apparently bacteriostatic rather than bactericidal.

F. H. Finlaison.

Surgery, Gynecology and Obstetrics.

Vol. lxviii, No. 3, March 1939.

*The diagonal conjugate *versus* X-ray pelvimetry. A. L. Dippel.

*Operative management of fibromyomata in the uterus at term. C. P. Huber and H. C. Hesseltine.

Vol. lxviii, No. 5, May 1939.

*Cervical stump carcinoma. M. E. Black.

*Carcinoma of Bartholin's gland; report of a case of squamous cell epithelioma. E. A. Simmendinger.

Vol. lxix, No. 1, July 1939.

*Ectopic pregnancy; a review of three hundred and ten operative cases. L. Langman and M. Goldblatt.

*A simple method for keeping dry bladder fistulae from cervix cancer. H. C. Saltzstein.

Vol. lxix, No. 2, August 1939.

*Results of attempted induction of labour with oestrin. S. Lubin and R. Waltman.

*Conservative myomectomy. B. Zondek.

THE DIAGONAL CONJUGATE VERSUS X-RAY PELVIMETRY.

Dippel states that the external conjugate measurement of the pelvis is a misleading obstetric procedure, and might well be discarded.

The diagonal conjugate measurement is of great value for the reason that this diameter, when greater than 11.5 centimetres, rules out antero-posterior

contraction of the pelvis. When it is less than 11.5 centimetres the information given by this measurement is of an approximate character only and X-ray pelvimetry is desirable. The author has found that the Hodge's stereoscopic method of X-ray pelvimetry gives an average error of ± 0.16 centimetre and a maximal error of ± 0.3 centimetre.

Operative Management of Fibromyomata in the Uterus at Term.

In the presence of fibromyomata during pregnancy there should be careful observation without interference unless symptoms of sufficient magnitude arise. Natural delivery should be allowed to go on unless the size, number or location of the tumours produce obstruction to the passage of the foetus. Doubtful cases should be submitted to a trial labour. If operative interference becomes necessary, Caesarean section should be performed with hysterectomy. If operative interference becomes necessary during the puerperium, hysterectomy is also the method of choice. Myomectomy with Caesarean section carries a greater mortality rate and should therefore be avoided.

Cervical Stump Carcinoma.

A clinical study of a series of cases of carcinoma of the cervix was undertaken by the author in view of the increasing number of cases of carcinoma cervicis seen following subtotal hysterectomy. It is interesting to note that stump cancer occurred in 8.1 per cent of cases, all following subtotal hysterectomy. The importance of pre-operative examination of the cervix, when hysterectomy is contemplated, especially the subtotal operation, is stressed. After the subtotal operation the patient's cervix should be examined at regular intervals, making use of all modern methods of examination.

Carcinoma of Bartholin's Gland.

In a review of cases of carcinoma of Bartholin's gland, reported by Simmendinger, it was found that the ages of the patients varied between 29 and 91. The average age was 51.6 years. Chronic infections of the gland are quite common and often lead to mistakes in diagnosis. In only one case was there a definite history of trauma to the gland; however, the glands undoubtedly must be the site of frequent trauma. Harer reports that the condition is commonly found in married women and may occur in unmarried women, but never in virgins. Carcinoma of Bartholin's gland is usually first noticed as a small, hard, painless nodular swelling lying deep in the labial fat. The skin is not involved until late and with enlargement of the tumour pain develops and is commonly referred to the coccyx and groin; it is made worse by coitus and menstruation. The most important points in diagnosis are the age of incidence, hardness of the tumour with tendency towards fixation, pain and, later, oedema of the vulva. Two types are possible, squamous cell epithelioma and adenocarcinoma. The prognosis is unfavour-

able owing to the almost uniform failure of early diagnosis. According to most authors proper treatment is a combination of radiation and surgery. Removal of the inguinal and femoral glands, followed by endothermic removal of the tumour with pre-operative and post-operative irradiation is perhaps the most suitable form of therapy.

The author gives a very full report of the case of a woman aged 74 years, who was admitted to the Cincinnati General Hospital and was operated upon for squamous cell carcinoma of Bartholin's gland by a complete excision of the vulva. The result 8 months after the operation was completely successful.

ECTOPIC PREGNANCY; A REVIEW OF THREE HUNDRED AND TEN OPERATIVE CASES.

Langmann and Goldblatt present a study of 310 cases in which patients were operated upon for ectopic pregnancy; or operated upon for some other condition and ectopic pregnancy found at operation, during seven years from 1930 to 1936, inclusive, at Bellevue Hospital.

There was an unusually high incidence of previous lower abdominal surgery. Although a history of pelvic infection was obtained in less than 20 per cent of the cases, microscopic examination of the Fallopian tubes showed evidence of inflammation in more than 50 per cent. The pain complained of was mostly colicky, severe, irregular and generalized over the abdomen. Radiation to one or both shoulders was relatively uncommon, but significant when present. Nausea and vomiting were more frequent than fainting. In doubtful cases a Friedman test was found to be indispensable; excluding abortion and normal intra-uterine pregnancy, a positive test always means an ectopic pregnancy. The use of repeated whole-blood transfusions before, during and after operation, should reduce the mortality to less than 2 per cent. More than two-thirds of the authors' cases occurred in the ampullary portion of the tube.

A SIMPLE METHOD FOR KEEPING DRY BLADDER FISTULAE FROM CERVIX CANCER.

When carcinoma cervicis ulcerates into the floor of the bladder a very disagreeable and uncomfortable condition ensues. Urologists have, during the past few years, made increasing use of continuous suction to carry off the urine draining from vesical wounds. Various devices have been described comfortably to fit on to the body surface in order to dispense with drainage tubes, or for use when tubes are not needed. In all such devices a gauze wick lies in the urine or secretion to be absorbed. Air is sucked through a perforated catheter tube or mask attached to the gauze. The suction pulls the urine through the gauze, into the tubing and then into a trap bottle. The author has used the Hendrickson catheter attached to Stedman electric suprapubic pump. This catheter ends in a flat spade-like tube, with 6 or 8 perforations on one side. A thick gauze wick is attached to the tube

and the free end moistened and inserted 3 or 4 inches into the vagina. The catheter remains outside the vagina and the tubing led over the thigh to a one-gallon drain bottle on the floor. The pump is attached to the other tube of the bottle. The vaginal wick must be changed every 1 or 2 days.

Results of Attempted Induction of Labour With Oestrin.

It has been shown that oestrin can initiate and maintain uterine motility and contractility in animals and humans. The authors made experiments and attempted to induce labour near, at, and beyond term by administration of oestrin without additional aid. Out of 36 patients, the onset of labour could be attributed to the injection of oestrin in 8 cases only. It is possible that the oestrin was responsible for short labours in 4 of the 9 primiparae in this series. The authors' findings, therefore, merely suggest the possibility that labour in the human, near, at, or beyond term, might be induced by the administration of oestrin and the duration of labour shortened.

Conservative Myomectomy.

Zondek states that in Germany he believed in the conservative point of view regarding operation on myoma, but during his practice in Palestine he has gone still further. The desire for a child is strong among women in Palestine, and the preservation of the uterus plays an important role. The author has, therefore, adopted a more conservative method of operation. Up to the present, in Jerusalem, he has performed 82 such operations, 40 of which were conservative. The conservative operation is justified only in women of a sexually mature age, i.e., up to 40 years. The technique of the conservative operation is more difficult than that of the supravaginal amputation or total extirpation of the uterus. Conservative myomectomy is atypical; once the abdomen is opened a plan must be made according to the case. It is not sufficient to remove the myomata, but in addition it is important to spare the musculature so far as possible in order to preserve a uterus capable of its function of pregnancy and parturition.

The important points in the operation are:—

(1) Every myoma must be enucleated. (2) The orifices of both Fallopian tubes, or at least one of them, must be spared. (3) The uterus must be reconstructed in such a manner as to preserve as much of the muscular tissue as possible.

In order to test this last point Zondek injects one ampule of posterior pituitary extract, pitocin, into the uterus at the end of the operation.

The objection to this conservative method is that the disease is not radically removed, but among the patients operated on in Palestine, Zondek saw only 2 recurrences.

Charles D. Read.

La Gynécologie

April, 1939.

*Haemorrhage at the time of delivery. Folke Holtz.

A new technique in the lower segment Caesarean section operation for use in infected cases. J. Courtois and Cl. Bouchacourt.

May, 1939.

*New researches into the action of testosterone on the genital tract of the doe. G. Cotte, J. F. Martin and Mme Mileff.

*Artificial development of the genitalia produced by the esters of testosterone. R. Moricard and F. Saulnier.

*The use of the male hormone in gynaecology with special reference to the treatment of haemorrhage. Turpault.

Haemorrhage at the Time of Delivery.

At the time of separation of the placenta a certain amount of bleeding occurs. This haemorrhage varies in quantity, the amount of blood lost depending on the contractility of the uterus. Haemostasis is produced by pressure on the vessels and not by thrombosis. The amount of blood lost varies according to different authors. Zangemeister estimated the loss at 170 to 180 c.c., Ashfield as high as 505 c.c., Stoeckel thought any loss between 200 to 400 c.c. could be regarded as normal. The general consensus of opinion is that any loss not exceeding 500 c.c. may be regarded as normal. Some women are less affected by a heavy loss than others: one woman's resistance may be better than another's. The author also shows the importance of the relation between the body weight, the total circulating blood, and the blood loss. The heavier the person, the greater is the volume of circulating blood and the better able is the patient to withstand the effects of blood loss.

Haemorrhage bears some relation to the area of the placental wound: a large child is likely to have a large placenta; this, on separation, leaves a large wound and predisposes to haemorrhage.

The author has studied 500 cases in Stockholm; only normal deliveries are included in his report.

He has tried to estimate the amount of blood lost per kilogramme of the body weight. Only rarely does a maternal loss as low as 1 c.c. per kilogramme of body weight occur. In 367 out of his total of 500 cases between 1 and 5 c.c. were lost. In only 128 cases were more than 5 c.c. per kilogramme lost. The author gives a table demonstrating that in 95.2 per cent of cases the blood loss is less than 10 c.c. per kilogramme body weight.

The author has also investigated the question of the relation of the size of the child and placenta to the blood loss. Ahlfeld and Schmid pointed out that the size of the foetus was of importance. The author confirms this observation. He points out that with a large mother, a large foetus is probable and a larger blood loss occurs than in a smaller person.

It has always been thought that older women were more disposed to

haemorrhage than younger. The author's observations show the reverse to be the case. Many authors, notably Boum, Spiers, Stroëder, have pointed out that haemorrhage is greater in multiparae than primiparae. The author's figures again demonstrate the reverse, and show that haemorrhage is certainly more marked in the primiparous group.

A woman who has had a previous miscarriage is no more liable to bleed than one who has not.

Another table shows that the blood loss varies with the duration of labour. Any woman who labours for more than 24 hours is predisposed to excessive loss.

The following points are stressed: That it is important to consider the total body weight of the patient; that the normal blood loss corresponds to between 2 and 3 c.c. per kilogramme of body weight; that up to 5 c.c. per kilogramme of body weight the loss may be considered normal; that the loss is greater with a large baby and less with a small one; that the age of the patient has no influence on the loss; that haemorrhage is more abundant in primiparae than multiparae; that difficult labour and delayed labour predispose to haemorrhage; that mild anaemia has no influence on the postpartum loss but a severe one with a haemoglobin estimation of below 60 per cent tends to be associated with severe loss; that a loss not exceeding 1000 c.c. can, in the presence of poor general resistance, cause the death of the patient, and that both a heavy loss and severe anaemia predispose to puerperal infections.

A long bibliography is given.

NEW RESEARCHES INTO THE ACTION OF TESTOSTERONE ON THE GENITAL TRACT OF THE DOE.

These authors published a paper in 1937 in which they showed that despite its chemical similarity to the female hormones, testosterone did not produce the same effects on the mammary gland and uterine cornua as progesterone and folliculin. The authors worked with castrated animals. Using folliculin, it was easy to produce hyperplasia in the uterine cornua and in the mammary glands. With testosterone this did not occur. In the non-castrated animal progesterone produced secretory changes; testosterone did not. Despite the negative results of this work the authors felt that testosterone had a real therapeutic value.

Cases of chronic mastitis and cases with irregular haemorrhage responded well to testosterone treatment, and the authors set out to discover whether any antagonism existed between folliculin and testosterone.

During this recent series of experiments only castrated animals were used. Some of the animals were treated with oestradial, others received injections of oestradial and progesterone, and others received oestradial and testosterone. The first animals, which had been treated with oestradial, showed well-marked necrotic lesions in the uterus at the end of two months. The lesions penetrated as far as the sub-endometrial tissues, and the vessels in the broken-down area were markedly altered and thrombosed. The authors feel

sure that this necrosis is due to the congestion caused by the folliculin and is vascular in type. On the edge of the necrosed type hyperplasia was marked. Thus, in 1937, working with non-castrated animals, injections of folliculin produced hyperplasia, but not necrosis. This year, working on castrated animals, marked necrosis ensued. The authors wanted to ascertain whether such necrosis could be prevented in the castrated animal by injections of testosterone.

The second animals were given 15 milligrammes of oestradial and 30 milligrammes of progesterone. Necrosis was not prevented by this dosage. The lesions, however, were not so obvious and the authors think that a larger dose of progesterone might have prevented any necrosis at all.

The third batch received oestradial and testosterone. Here some necrosis occurred and the appearances were very similar to those in Group II. One animal, however, received a double dose of testosterone, 150 milligrammes of testosterone to 15 milligrammes of benzo-gynoestryl, and necrosis did not occur. The authors regard this as of extreme importance. If the dosage of testosterone be large enough the effects of the folliculin are neutralized. Results with testosterone have only been obtained with large doses. It is probable that analogous results would have occurred with large doses of progesterone. The authors suggest that further experiments should be performed with testosterone and progesterone to assess the reaction of each with folliculin.

ARTIFICIAL DEVELOPMENT OF THE GENITALIA PRODUCED BY THE ESTERS OF TESTOSTERONE.

It is known that the esterification of folliculin augments its activity, so Tschopp carried out experiments with the male hormone, and showed that two esters of the latter, the acetate and the propionate, are particularly active. The reader is reminded of the physiological action of testosterone. Castration in the male produces a rapid retrogression of the genital tract and the comb in cock birds. The injection of testosterone produces development in the penis, prostate, vesiculae seminales, and in the secondary sex characteristics. Profound changes in the anterior pituitary also occur after castration. Some examples of the therapeutic action of testosterone are given. In male children with under-development of the genitalia testosterone produces marked change in the size of the penis, in the development of the pubic hair, in the general build and the psyche. The authors have employed this hormone on the castrated human female, and speak highly of its therapeutic value. Hot flushes are often completely controlled during the week following an injection of 5 or 10 milligrammes of the testosterone ester preparation. Patients become more cheerful, more active, sleep better and feel markedly improved. Patients no longer complain of forgetfulness.

Intramuscular injection of testosterone often helps to control pruritus vulvae. The hormone has little effect on the development of the female genital tract and does not produce any uterine or vaginal hyperplasia in patients who have had their ovaries removed.

THE USE OF THE MALE HORMONE IN GYNAECOLOGY WITH SPECIAL REFERENCE TO THE TREATMENT OF HAEMORRHAGE.

Testosterone is of use in the treatment of haemorrhage due to fibroid tumours and hormone malfunction: after the first injection the bleeding diminishes. During treatment the patients may complain of lassitude, excitement, a deepening of the voice or enlargement of the clitoris. In the treatment of fibroids the rapidly growing vascular type of growth reacts much better than an old-standing one. Chronic mastitis is often benefited by the hormone. Small doses should be exhibited for mammary conditions, larger doses for malfunctional bleeding, and larger ones again in the treatment of fibroids. Sometimes symptoms reappear after the injections are stopped and in these cases the hormone may be implanted in the tissues in its crystalline form as advised by Parkes.

C. E. B. Rickards.

Gynécologie et Obstétrique.

Vol. xxxix, April, 1939, No. 4.

*The action of chloroform on the uterine contractions. Lévy-Solal, M. Sureau.
The dangers of artificial delivery. J. Rhenter, H. Magnin.
*The difficulties of delivering the head in the lower segment Caesarean operation. H. Vermelin, J. Louyot.
Heliotherapy in the treatment of genital tuberculosis. A. Aimes.
The surgical treatment of spreading post-abortive peritonitis. E. Rochet, C. Ambre.
*The treatment of eclampsia. Gellé.

THE ACTION OF CHLOROFORM ON THE UTERINE CONTRACTIONS.

Lévy-Solal and Sureau show and discuss graphs of the uterine contractions under chloroform anaesthesia.

Under moderate anaesthesia the contractions are less frequent, shorter and less intense and they lose their expulsive character. The action of chloroform is almost immediate, but on the other hand, there is an interval of 10 to 20 minutes after the cessation of the administration of the chloroform before contractility returns.

Even under light chloroform analgesia a definite inhibition of uterine tone is observed.

In threatened contraction, as for instance after the injudicious administration of pituitrin, chloroform has a specifically beneficial effect far greater than that produced by morphia or any of the recognized uterine antispasmodics.

DELIVERY OF THE HEAD IN THE LOWER SEGMENT CAESAREAN OPERATION.

Vermalin and Louyot discuss the difficulties which may be experienced in the delivery of the foetal head in this operation. Since the head is usually lying in the transverse diameter of the inlet and as often as not in a position of anterior asynclitism a formal rotation is necessary, and the head is usually best delivered as a face presentation. As soon as the head is exposed they effect this conversion by inserting a finger into the child's mouth. For cases in which the head is very mobile and more traction is required they have devised a special forceps modelled on Faraboeuf's instrument, because the various tenacula forceps employed for this purpose proved unsatisfactory.

In their instrument the blades are mounted at right angles to the shanks. One of the handles is long and the other is short, so that the articulated forceps lies flat in one plane. A traction rod is fixed to the longer or female blade at the junction of the blade and the shank. The authors claim that with this forceps the mechanisms of a normal delivery can be very accurately copied.

THE TREATMENT OF ECLAMPSIA.

Gelle describes six cases in full detail, giving the exact figure of the blood chemistry in each case. His article should be of value to workers in the biochemistry of eclampsia.

REPORTS OF SOCIETIES.

THE ROYAL SOCIETY OF MEDICINE.

At a meeting of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine, held at the Society's house on Friday, March 17th, 1939, at 8 p.m., the President, Mr. ALECK BOURNE, was in the chair.

Professor ALEXANDER FLEMING read a paper on

THE SYNERGIC ACTION OF VACCINE AND SERUM THERAPY AND TREATMENT WITH SULPHANILAMIDE AND M & B 693.

It has been shown that sulphanilamide and 693 have essentially a bacteriostatic rather than a bactericidal action. The actual destruction of the bacteria has therefore mainly to be by the natural defensive mechanisms of the body. A series of experiments was undertaken to demonstrate that the action of these drugs was much enhanced if appropriate antisera were given at the same time. A similar series of experiments showed that an active immunity produced by vaccines also greatly assisted their action.

Professor F. J. BROWNE, Mr. D. H. MCLEOD, Mr. WYATT, Dr. LOWENTHAL and the President took part in the discussion.

Dr. B. L. WILLIAMS, Mr. R. C. PERCIVAL and Mr. S. G. CLAYTON read three short papers on

THE EFFECT OF THE INJECTION OF FIVE UNITS OF PITUITARY EXTRACT IMMEDIATELY AFTER DELIVERY OF THE FOETUS.

A small series of cases with appropriate controls was considered in each paper, and although the results varied the general conclusions were that the duration of the third stage of labour was not appreciably affected and that the tendency to postpartum haemorrhage was reduced.

Professor CHASSAR MOIR showed

A SHORT FILM TO DEMONSTRATE THE EFFECT OF OXYTOXIC DRUGS ON THE UTERUS AND THE ADVANTAGES OF DIRECT INJECTION INTO THE UTERUS.

Mr. WYATT, Mr. BOURNE, Mr. NICHOL, Dr. DOROTHY LOGAN and Professor LOWRY (Belfast) took part in the discussion.

Dr. G. F. ABERCROMBIE read a paper on

THE ELIMINATION OF BREECH PRESENTATION FROM PRIVATE PRACTICE

which showed the advantages of version before the thirty-second week of pregnancy.

Mr. WRIGLEY and Mr. VARTAN took part in the discussion.

Professor CHASSAR MOIR demonstrated

A NEW OBSTETRIC BED

which he has designed.

At the annual general meeting of the Section of Obstetrics and Gynaecology of the Royal Society of Medicine, held at the Society's house, 1, Wimpole Street, W.1, on Friday, May 19th, 1939, at 8 p.m., the President, Mr. ALECK BOURNE, was in the Chair.

Professor F. J. BROWNE showed

A GIRL NOW AGED 12 WHO WAS DELIVERED FROM THE ABDOMEN IN A CASE OF FULL TIME ECTOPIC PREGNANCY.

During pregnancy the mother had some colicky pain about the sixteenth week, but otherwise there were no serious symptoms during pregnancy. At the thirty-sixth week a transverse lie was observed, and an attempt at version failed. It was decided to perform a Caesarean section at term.

The correct diagnosis was not made until the gestation sac was opened. The placenta was attached to the left side of the uterus and the left broad ligament. The placenta was removed and bleeding was easily controlled. Four years later the mother had a normal intra-uterine pregnancy.

Mr. LESLIE WILLIAMS, Mr. GORDON LUKER, Mr. JAMES WYATT, Mr. L. CARNAC RIVETT, Mr. ALBERT DAVIS and Mr. C. M. GWILLIM spoke.

Professor F. J. BROWNE read a short communication.

TWO CASES ILLUSTRATING THE DANGER OF WILLETT'S FORCEPS IN PLACENTA PRAEVIA.

He described two recent cases in which the mother and the foetus had become infected with bacillus Welchii. He maintained that the conditions produced by the use of Willett's forceps particularly predisposed to this infection, as the foetus frequently died and the wound produced by the forceps made a point of entry for the organisms to the dead tissues of the foetus, and so to the mother.

In the cases described one of the mothers died.

Mr. C. M. GWILLIM, Mr. J. P. HEDLEY, Mr. L. CARNAC RIVETT, Mr. LESLIE WILLIAMS and Mr. G. F. GIBBERD took part in the discussion.

Mr. ALBERT DAVIS read a paper on

THE DIAGNOSTIC VALUE OF HYSTEROGRAPHY IN GYNAECOLOGY (STERILITY EXCLUDED).

The paper was illustrated by a large number of hysterograms.

He began by illustrating the variations which may occur in the appearance of the normal uterus and the appearances which may be produced by contractions of the uterus, and pointed out that considerable experience is necessary in interpreting the hysterograms.

The appearances produced by a large number of abnormal conditions were illustrated, including fibroids, placental polypi, and carcinoma of the body of the uterus.

He pointed out that his chief object in presenting this paper was to illustrate what could be done by hysterography. He did not imply that he considered this the best method of diagnosis in all the conditions he illustrated.

Professor F. J. BROWNE, Professor CHASSAR MOIR and the President spoke.

Mr. J. ST. GEORGE WILSON showed two films. The first showed

THE DELIVERY OF THE LIVERPOOL QUADRUPLETS.

The diagnosis was made during pregnancy by means of X-rays. All four, three males and a female, were delivered by the breech. All four were delivered within 15 minutes, and the placenta followed shortly afterwards without any undue bleeding. All four were born alive and weighed 3, 5, 4, 4 pounds respectively. Two died within a few days. The film was in colour, and all four foetûs and the placenta were delivered before the umbilical cord was cut.

Mr. J. ST. GEORGE WILSON's second film showed

THE OPERATION OF AMPUTATION OF THE CERVIX WITH THE DIATHERMY CAUTERY.

Mr. L. CARNAC RIVETT, Mr. J. HOWKINS and Miss BLOOMFIELD spoke.

Mr. G. F. GIBBERD read a short communication on

THE FACTORS INFLUENCING THE ATTITUDE OF THE FOETUS IN UTERO.

He pointed out that the attitude of the foetus in the uterus was only constrained to a limited extent by the shape of the uterus. Clearly there

was not enough room for the foetus to adopt an attitude of full extension of the limbs, but as a rule the foetus tended to adopt an attitude of flexion even in cases of hydramnios, when there was ample room for it to extend. He next showed a number of radiograms to illustrate the rotation of the head sometimes seen in breech presentation. Finally he showed a number of cases in which the foetus assumed an attitude of extreme extension during pregnancy, and showed that frequently the foetus, although not spastic, preferred this attitude for some time after birth. He thought that the attitude of the foetus depended largely on slight differences between the tone of the flexor and extensor muscles.

In the discussion which followed, Mr. WINTERTON, Mr. KELLAR and Mr. KNOWLTON showed photographs of similar cases of extreme extension of the foetus.

Professor YOUNG took part in the discussion.

Mr. J. H. PEEL read a short communication on

PERSISTENT MENSTRUATION UNTIL THE AGE OF 71.

The patient had started menstruating at the age of 15. At the age of 40 she missed three periods, but since that time she had continued to menstruate regularly. She complained of excessive menstruation for 5 months and a feeling of weight in the pelvis. On examination she was found to have a tumour reaching nearly to the umbilicus. At laparotomy the tumour was found to arise from the right ovary. The uterus was removed by panhysterectomy together with both Fallopian tubes and both ovaries. Examination of the specimen showed that the tumour was a fibro-sarcoma. There was no evidence of granulosa cells. There was some hypertrophy of an apparently normal menstrual endometrium.

Mr. J. H. PEEL read a paper on

THE EFFECTS OF STILBOESTROL ON LABOUR.

In a series of 79 cases, doses of from 10 to 50 milligrams were given. In 50 cases a slight reduction in the duration of labour was observed In 16 cases stilboestrol was used with a view to inducing labour, with six successes. The effect of the hormone was also tried in cases of inertia during labour with success in about half the cases.

SIR COMYNS BERKELEY and Mr. KELLAR took part in the discussion.